American Institute of Integrative Oncology
RESEARCH & EDUCATION

Foundations of Integrative Oncology
COURSE

GRAND ROUNDS CALL
With Dr. Nalini Chilkov
January 9th, 2019
Second Wednesday of Every Month
5:30 PM Pacific / 6:30 PM Mountain / 7:30 PM Central / 8:30 PM Eastern

Clinical Pearl: Managing Side Effects of Platinum Chemotherapy Drugs PART ONE

See PDF Slides Attached

Case Study: 44yo F Metastatic Breast Cancer

Submitted by: *Monica Sood MD*

Overview: 44 yo Indian American F 142 lbs, insulin resistant, Dx 06/2018 ER+ PR+ her2 neu+ BrCA Metastatic to L femur (post fixation and RT) , post L mastectomy, post CT=Paclitaxel (peripheral neuropathy), post salpingo-oopherectomy, osteopenic R hip, Current tx Letrozole, Trastuzumab, Pertuzumab, Xgeva, lexapro, Current: Normal PET scan, hsCRP 5.17, Vit D 60, normal tumor markers, Acupuncture, meditation, prayer, Sees Dietician

Core Questions:

- How to Prevent recurrence?
- If unable to tolerate letrozole (joint pain) what is alternative?

Recommendations:
See Attached Documents: Case study submission and Dr. Chilkov's Comments

Case Study Follow-up Questions from Dr. Sood:

Question: Should my patient finish her beta glucan (she has several vials left)
Dr. Chilkov's response: Absolutely, yes, no contraindication

Question: Does she need to do copper chelation?
Dr. Chilkov's response: Must measure biomarkers CBC + Diff, Ceruloplasmin, Serum Cu, Serum Zinc to assess need/value.
ALSO…There is a clinical pearl on oral Cu Chelation with slides and references from last year…more thorough discussion.

Question: Does AHCC work well with chelation?
Dr. Chilkov's response: No interactions…no benefits or risks. AHCC primarily supports NK, WBC, neutrophils…but not RBCs which are lowered during Cu Chelation. Therefore you need to monitor CBC + Diff and Cu and Cp during oral Cu Chelation for RBC anemia. If RBC anemia persists, take a break from Cu Chelation and counts bounce right back CANNOT do oral Cu chelation with RBC anemia, myelosuppression

***Question*:** Can you send me the protocol for the daily tumor control?
***Dr. Chilkov's response*:** There is a copy of the tx plan uploaded to our library on the AIIORE site.

Research: Brain Exercises for Cognitive Decline in Breast Cancer Survivors

Weinstein Kaplan, Bette

Brain Exercise Program Eases Chemobrain in Breast Cancer Survivors

Oncology Nurse Adviser Dec 24 2018

Breast cancer survivors experience significant deficits in memory compared with women who did not have cancer.

Through his studies on brain plasticity, Dr Merzenich developed computerized brain training exercises that could rewire the human brain through intensive adaptive practice, leading to a brain that is faster and more accurate — and as a result, has sharper cognitive abilities.

National Cancer Institute designates BrainHQ as a research-tested intervention program. San Francisco, CA: Posit Science; November 5, 2018. https://globenewswire.com/news-release/2018/11/05/1644999/0/en/National-Cancer-Institute-Designates-BrainHQ-as-a-Research-Tested-Intervention-Program.html

Cognitive Training and Chemobrain. brainHQ website. https://www.brainhq.com/partners/resources/nci.

Research: ROYAL JELLY

Available in capsules

Recommended oral dose: 1-3 grams/day

Can also be used topically for oral mucositis

Anti-Cancer and Protective Effects of Royal Jelly for Therapy-Induced Toxicities in Malignancies

Yasuyoshi Miyata and Hideki Sakai*

Int J Mol Sci. 2018 Oct; 19(10): 3270. Published online 2018 Oct 21. doi: 10.3390/ijms19103270 https://dx.doi.org/10.3390%2Fijms19103270

Summaries of studies on the anti-cancer effects of RJ reported in in vivo and in vitro.

RJ and its main component, 10-HDA, can **inhibit tumor growth and cancer cell invasion** via the regulation of various cancer-related factors.

In addition, animal experiments have shown that RJ administration leads to **prolonged survival** with a variety of malignancies. Many reports demonstrated that RJ is **useful for protection against anti-cancer agent-induced toxicities, such as mucositis, fibrosis and disorder of the kidney and the liver.**

Furthermore, the **modulation of various biological activities by RJ, including cell survival, inflammation and oxidative stress, is closely associated with the RJ-induced effects.**

Several clinical studies have confirmed the **efficacy of RJ against drug-induced toxicities and clarified the mechanisms in patients with cancer;** however, almost all of these clinical trials used relatively small study populations. Therefore, more detailed investigations are essential for a discussion of the clinical utility

of RJ in these patients. The efficacy and safety of various combination therapies based on RJ and anti-cancer drugs, using various fractions of RJ, have been reported in vivo and in vitro. Although it is certain many problems remain to be solved, we believe that **RJ is a potential tool for the improvement in the QOL and prognosis of patients treated with anti-cancer therapies.**

Managing Side Effects of Platinum Chemotherapy Drugs PART ONE

Oxidative Stress
Nephrotoxicity
Neurotoxicity
Myelosuppression
Hypo-magnesia
Hepatotoxicity

Dr. Nalini Chilkov, Founder

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Overview | Platinum Drugs

Cisplatin Carboplatin Oxaliplatin

- Prescribed in a wide range of cancers
- Use is limited by toxic side effects and adverse events
- The side effects may require patients to be prescribed dose reductions of between 25 and 100%
- A cancer patient can experience any combination of up to 40 specific side effects
- Patients require extensive monitoring of their biochemistries, kidney, liver, cardiac function (ejection fraction, ECG), hearing tests

Mechanisms of Action | Platinum Drugs

Cisplatin Carboplatin Oxaliplatin

Alkylating Agents

- Form DNA Adducts
- Pro Oxidant
- Pro Inflammatory
- Promote Cell Cycle Arrest
- Promote Apoptosis
- Promote Necrosis

Adverse Effects | Platinum Drugs

DNA Damage-Oxidative Stress-Inflammation

- Neurotoxicity-Ototoxicity
- Cardiotoxicity
- Nephrotoxicity
- Hypomagnesia
- Hematologic Toxicity
- Mito-Toxicity
- Gastrointestinal Toxicity
- Hepatotoxicity
- Hypercoagulation-Thrombosis
- Fatigue
- Cachexia
- Alopecia

The side effects of platinum-based chemotherapy drugs: a review for chemists
Dalton Transactions 21 May 2018, Issue 19, 6635 to 6870 Rabbab Oun, et al

OXIDATIVE STRESS

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Oxidative Stress | Antioxidants and Chemotherapy

174 peer-reviewed original articles from 1967-2017 comprising 93 clinical trials with a cumulative number of 18,208 subjects,

- **Antioxidants do not interfere with chemotherapy**
- **Antioxidants mitigate the toxicities induced by chemotherapeutic agents**
- **The therapeutic efficiency of chemotherapy increases in the presence antioxidants**
- **Antioxidant supplementation was also seen to increase survival time**

Saudi Pharm J. 2018 Feb; 26(2): 177–190. doi: 10.1016/j.jsps.2017.12.013 Antioxidants as precision weapons in war against cancer chemotherapy induced toxicity – Exploring the armoury of obscurity. Kanchanlata Singh et al

Integr Cancer Ther. 2016 Mar; 15(1): 17–39. doi: 10.1177/1534735415610427
Efficacy and Interaction of Antioxidant Supplements as Adjuvant Therapy in Cancer Treatment A Systematic Review. Asuka Yasueda, et al

Phase III RCT on Vitamin E and Cisplatin-Induced Neuropathy

(Neurology. 2010 Mar 2;74(9):762-6)

Vitamin E: 400-800 IU. qd

- Of 108 randomized patients, 68 received at least one clinical and neurophysiologic examination after cisplatin
- 41 patients received a cumulative dose of cisplatin higher than 300 mg/m(2) and were eligible for statistical analysis: 17 in the vitamin E group (group 1) and 24 in the placebo group (group 2).
- The incidence of neurotoxicity was significantly lower in group 1 (5.9%) than in group 2 (41.7%) ($p < 0.01$).
- The severity of neurotoxicity, measured with a validated neurotoxicity score (Total Neuropathy Score [TNS]), was significantly lower in patients receiving vitamin E than those receiving placebo (mean TNS 1.4 vs 4.1; $p < 0.01$).

HEMATOLOGIC TOXICITY
MYELOSUPPRESSION

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Hematologic Toxicity | Myelosuppression (Carboplatin) Monitor CBC + Differential

Acupuncture-Moxabustion	Su San Li, St.36 qd
Neutropenia Leukopenia	Astragalus (Huang Qi) 3g qd Acupuncture
Thrombocytopenia	Marrow Plus 3 tid or Immucare I 3 tid Melatonin 20mg qd hs and Ceonothus americanus Red Root 3g qd
Anemia	Marrow Plus 3 tid or Immucare 13 tid Acupuncture

Marrow Plus or Immuncare I	3 tid
Shih Chuan Da Bu Tang	3-6 grams qd

Hematologic Toxicity | Myelosuppression
Acupuncture and Moxabustion
Acupoint Su San Li (Stomach 36)

J Altern Complement Med. Jul 2009; 15(7): 745–753.
Acupuncture for Chemotherapy-Induced Neutropenia in Patients with Gynecologic Malignancies: A Pilot Randomized, Sham-Controlled Clinical Trial

Weidong Lu, et al.
Treatment of chemotherapy-induced leukocytopenia with acupuncture and moxibustion Chung Hsi i Chieh Ho Tsa Chih Chinese Journal of Modern Developments in Traditional Medicine, 1991 Jun, 11(6):350-2, 325. Language: Chinese.

Effect of acupuncture on interleukin-2 level and NK cell immunoactivity of peripheral blood of malignant tumor patients Chung-Kuo Chung Hsi i Chieh Ho Tsa Chih, 1994 Sep, 14(9):537-9. Language: Chinese. (ul: 95170260) Pub type: Clinical Trial; Journal Article; Rand Controlled Trial

Polysaccharide Rich Botanicals with Hematopoetic Effects

2-4g qd

Rhodiola rosea
Angelica sinensis
Lycium barbarum
Astragalus memb.
Polygonum multiflorum
Epimedium grandiflorum
Tremella fuciformis
Grifolia frondosa
Ganoderma lucidum
Cordyceps sinensis
Coriolus versicolor

Immunomodulatory and anti-tumour polysaccharides from medicinal plants. Wong CK et al Biomed 2014 Sep 2.Medicinal mushroom science: Current perspectives, advances, evidences, and challenges.

Oxaliplatin-based chemotherapy combined with traditional medicines for neutropenia in colorectal cancer: A meta-analysis of the contributions of specific plants. Chen M,et al. Crit Rev Oncol Hematol. 2016 Sep;105:18-34.

NEPHROTOXICITY

Nephrotoxicity | Hypomagnesia

Mg Glycinate 300mg tid

Hypomagnesemia is known to occur in 29% to100% of patients undergoing platinum based chemotherapy

Prophylactic IV Mg in pre- and post hydration followed by oral Mg supplementation can play an important role in preventing platinum induced serum hypomagnesemia.

Clinical signs and symptoms: loss of appetite, nausea, vomiting, headache, weakness, numbness, tingling, muscle cramps, constipation, fatigue, anxiety, restless legs, insomnia, depression, irritability, asthma, refractory hypocalcemia and hypokalemia, high blood pressure, tremor, tetany, prolonged QT interval, cardiac arrhythmias, ataxia, carpopedal spasms, seizures, metabolic alkalosis, psychiatric disturbances, and cortical blindness.

Natural Med J October 2015 Vol. 7 Issue 10 Identifying and Treating Magnesium Deficiency in Cancer Patients Receiving Platinum-based Chemotherapy :A review of the literature on hypomagnesemia in cancer patients Jen Green, ND, FABNO, Meighan Valero, ND, Laura Perkowski, ND

Nephrotoxicity Hypomagnesia (Cisplatin)

Magnesium Glycinate 300mg tid

Monitor Serum RBC Magnesium + S&S

Life Sci. 2017 Nov 15;189:18-22. doi: 10.1016/j.lfs.2017.08.028. Epub 2017 Aug 31.

Magnesium co-administration decreases cisplatin-induced nephrotoxicity in the multiple cisplatin administration. Saito Y, Okamoto K et al

Eur J Pharmacol. 2017 Sep 15;811:191-198. doi: 10.1016/j.ejphar.2017.05.034. Epub 2017 May 18.

Magnesium attenuates cisplatin-induced nephrotoxicity by regulating the expression of renal transporters. Saito Y[1], Okamoto K[2], et al

Cisplatin (CDDP)-induced nephrotoxicity (CIN) is one of the most serious toxicities caused by this potent antitumor agent. It has been reported that Mg premedication attenuates CIN in clinical trials

****murine studies****

Nephrotoxicity
Milk Thistle: Silibinin & Silymarin 1-3g q d

Potential renoprotective effects of silymarin against nephrotoxic drugs: a review of literature. Dashti-Khavidaki S, Shahbazi F, Khalili H, Lessan-Pezeshki M. J Pharm Pharm Sci. 2012;15(1):112-23. Review.

Silymarin selectively protects human renal cells from cisplatin-induced cell death. Ninsontia C, Pongjit K, Chaotham C, Chanvorachote P.Pharm Biol. 2011 Oct;49(10):1082-90. doi: 10.3109/13880209.2011.568506. Epub 2011 May 18.

Silibinin protects against cisplatin-induced nephrotoxicity without compromising cisplatin or ifosfamide anti-tumour activity.
Bokemeyer C, Fels LM, Dunn T, Voigt W, Gaedeke J, Schmoll HJ, Stolte H, Lentzen H. Br J Cancer. 1996 Dec;74(12):2036-41.

Nephrotoxicity

L-Carnitine 1000mg bid-tid

N Acetyl Cysteine 500-1000mg bid-qid

Silymarin 3g/day

Potential nephroprotective effects of l-**carnitine** against drug-induced nephropathy: a review of literature. Jafari A et al Expert Opin Drug Saf. 2013 Jul;12(4):523-43. doi: 10.1517/14740338.2013.794217. Epub 2013 May 8. Review.

Effect of **Silymarin** Administration on Cisplatin **Nephrotoxicity**: Report from A Pilot, Randomized, Double-Blinded, Placebo-Controlled Clinical Trial.
Shahbazi F et al; Phytother Res. 2015 Jul;29(7):1046-53. doi: 10.1002/ptr.5345. Epub 2015 Apr 7.

Dose escalation study of intravenous and intra-arterial N-**acetylcysteine** for the prevention of oto- and **nephrotoxicity** of cisplatin with a contrast-induced nephropathy model in patients with renal insufficiency.
Dósa E, et al Fluids Barriers CNS. 2017 Oct 3;14(1):26. doi: 10.1186/s12987-017-0075-0.

Nephrotoxicity
Protective Effects of Royal Jelly

- Preservation of normal renal function
- Reduced renal fibrotic and histologic changes
- Reduced oxidative stress
- Inhibited elevation of serum creatinine, urea, uric acid

Yasuyoshi Miyata, Hideki Sakai
Anti-Cancer and Protective Effects of Royal Jelly for Therapy-Induced Toxicities in Malignancies.
Int. J. Mol. Sci. **2018,** 19, 3270

Silici, S.; Ekmekcioglu, O.; Kanbur, M.; Deniz, K. **The protective effect of royal jelly against cisplatin-induced renal oxidative stress in rats**. World J. Urol. 2011, 29, 127–132.

Ibrahim, A.; Eldaim, M.A.; Abdel-Daim, M.M.
Nephroprotective effect of bee honey and royal jelly against subchronic cisplatin toxicity in rats. Cytotechnology 2016, 68, 1039–1048.

Nephrotoxicity | Oxidative Stress. (Cisplatin)

Monitor Serum BUN, Potassium, Creatinine, GFR

Silymarin 3g q d Melatonin 20 mg hs

Curr Pharm Des. 2015;21(7):936-49.
Melatonin and renal protection: novel perspectives from animal experiments and human studies (review).
Hrenak J, Paulis L, Repova K, Aziriova S, Nagtegaal EJ, Reiter RJ, Simko F1.

Asian Pac J Cancer Prev v.18(2); 2017. doi: 10.22034/APJCP.2017.18.2.295
Cisplatin-Induced Nephrotoxicity; Protective Supplements and Gender Differences. Mehdi Nematbakhsh et al

Effect of **Silymarin** Administration on Cisplatin **Nephrotoxicity**: Report from A Pilot, Randomized, Double-Blinded, Placebo-Controlled Clinical Trial.
Shahbazi F et al; Phytother Res. 2015 Jul;29(7):1046-53. doi: 10.1002/ptr.5345. Epub 2015 Apr 7.

NEUROTOXICITY

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Neurotoxicity

CNS Neurotoxicity: Cognitive Impairment
Peripheral Neuropathy: Sensory-Motor
Ototoxicity (Oxaliplatin)

Acetyl L Carnitine	1g bid-tid
L Glutamine	5g bid-tid
Omega 3 Fatty Acids	2000mg bid
Melatonin	10-20mg hs
Benfotamine	100mg bid- tid
MethylCobalamin	1-2mg bid-tid
Stabilized R Lipoic Acid	500-1000mg tid-qid
Liposomal Glutathione	4 pumps s/l tid-qid
Acupuncture	1-3x/week

Neurotoxicity CIPN GLUTATHIONE
Chemotherapy Induced Peripheral Neuropathy

Neuroprotective effect of reduced glutathione on cisplatin-based chemotherapy in advanced gastric cancer: a randomized double-blind placebo- controlled trial.
Cascinu S, et al1995;13(1):26–32

Glutathione reduces the toxicity and improves quality of life of women diagnosed with ovarian cancer treated with cisplatin: results of a double-blind, randomised trial. Smyth JF, Bowman et al. Ann Oncol.1997;8(6):569–573

Neurotoxicity ACETYL L CARNITINE. 1-4g qd Chemotherapy Induced Peripheral Neuropathy

Mestri A, et al **A pilot study on the effect of acetyl-L-carnitine in paclitaxel- and cisplatin-induced peripheral neuropathy.** Tumori. 2005;91(2):135–138

Hershman DL,et al. **Randomized placebo-controlled trial of acetyl-L-carnitine for prevention of taxane-induced neuropathy during adjuvant breast cancer therapy.**
J Clin Oncol. 2012;Suppl.:abstr 9018:

Bianchi G, et al. **Symptomatic and neurophysiological responses of paclitaxel- or cisplatin-induced neuropathy to oral acetyl-L-carnitine.**
Eur J Cancer. 2005;41(12):1746–1750

Neurotoxicity N-ACETYLCYSTEINE
Chemotherapy Induced Peripheral Neuropathy

DOSE 1200mg NAC q d

Support Care Cancer. 2006 May;14(5):484-7
N-acetylcysteine has neuroprotective effects against oxaliplatin-based adjuvant chemotherapy in colon cancer patients: preliminary data. Lin PC et al

Neurotoxicity L-GLUTAMINE
Chemotherapy Induced Peripheral Neuropathy

DOSE: 15g bid x 7 consecutive days
starting on day 1 of oxaliplatin tx

Oral glutamine significantly reduces the incidence and severity of peripheral neuropathy of Metastatic CRC patients receiving oxaliplatin without affecting response to chemotherapy and survival.

Oncologist. 2007 Mar;12(3):312-9.
Oral glutamine is effective for preventing oxaliplatin-induced neuropathy in colorectal cancer patients. Wang WS, et al

HEPATOTOXICITY

Hepatoxicity

Monitor Liver Function (AST, ALT, ALK PHOS, GGT)

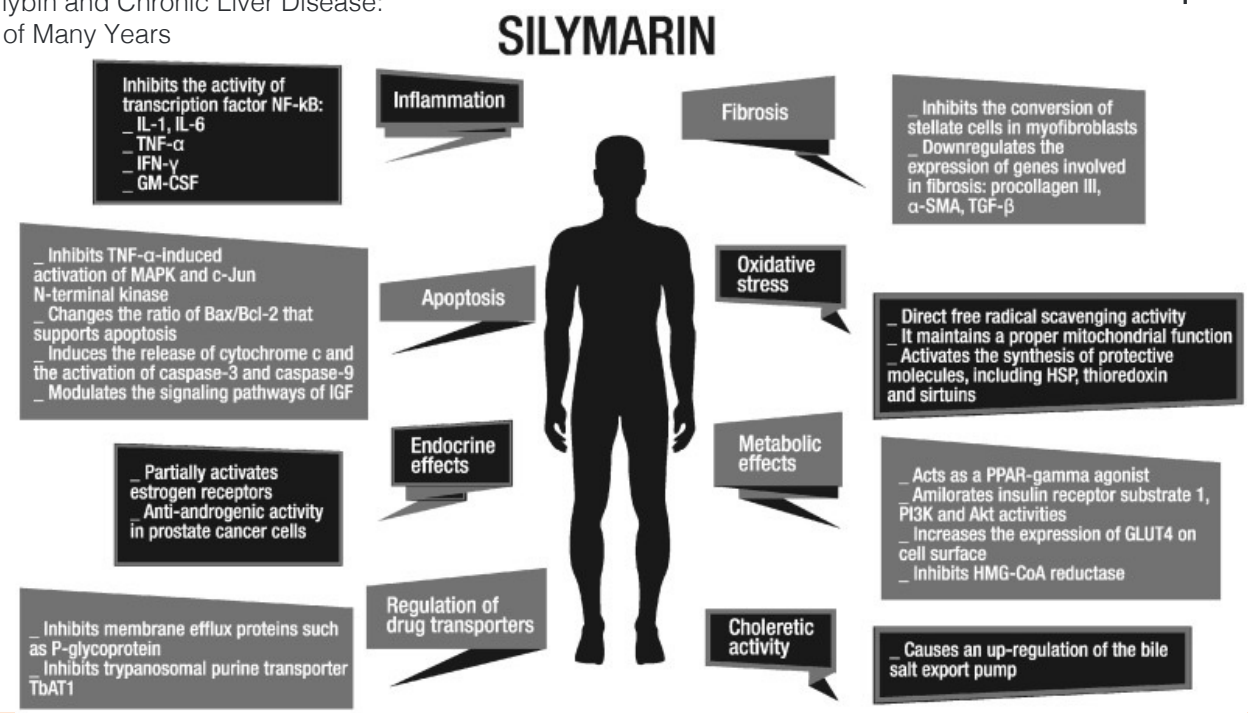
Silymarin - Milk Thistle 4 g/day

N-Acetyl Cysteine 2-4 g/day

Glutathione oral S-Acetyl Glutathione 200-400mg bid
or oral Liposomal Glutathione

Molecules. 2017 Feb; 22(2): 191.
Silymarin/Silybin and Chronic Liver Disease:
A Marriage of Many Years

1-3 t qd



N-AcetylCysteine is an Antidote Against Hepatotoxicity 2-4g qd

- Anti-inflammatory reduces hepatic TNF-α and IL-6
- Anti-Oxidant
- Increases hepatic and serum levels of Glutathione (GSH)
- Glutathione:Oxidized Glutathione ratio
- Increases liver and serum activities of Glutathione Reductase and Glutathione-S-Transferase
- Acts as a source of cysteine for GSH synthesis

Int J Mol Sci. 2015 Dec 18;16(12):30269-308.
Oxidative Stress and Inflammation in Hepatic Diseases: Therapeutic Possibilities of N-Acetylcysteine. de Andrade KQ

Hepatotoxicity 1-3g qd
Protective Effects of Royal Jelly

- Lower serum ALT concentrations
- Anti-apoptotic
- Anti-oxidant
- Free Radical Scavenging
- Increase in Super Oxide dismutase, catalase, glutathione peroxidase

Yasuyoshi Miyata, Hideki Sakai
Anti-Cancer and Protective Effects of Royal Jelly for Therapy-Induced Toxicities in Malignancies. Int. J. Mol. Sci. **2018,** 19, 3270

Karadeniz A., Simsek N., Karakus E., Yildirim S., Kara A., Can I., Kisa F., Emre H., Turkeli M. **Royal jelly modulates oxidative stress and apoptosis in liver and kidneys of rats treated with cisplatin**. Oxid. Med. Cell Longev. 2011;2011:981793. doi: 10.1155/2011/981793

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CASE STUDY SUBMISSION

Important: In observance of HIPAA and the sacred trust between care giver and patient, absolutely no patient names or identifying information is to be disclosed. Patient privacy is to be preserved. If you attach any medical records, pathology, surgical or laboratory reports, all names are to be removed.

Date	12/13/18
Clinician Name & Credentials	Monica Sood, MD
Email	monicasoodmd@gmail.com

Describe Your Patient (Please SUMMARIZE and use economy of words. You will have 15 minutes to present)

Age, Gender & Ethnicity	44 yo Indian American
Body Type	Slender 142 lbs
Values *What is most important to this patient? (Quality of Life, Decision Making, Side Effects?)*	Preventing breast cancer recurrence Good quality of life Managing side effects of letrozole
Stress Resilience	Difficult: history of anxiety & depression since 25
Other	
Primary Diagnosis & Date *(ex. Breast Cancer L, T3 N1 M0, BRCA1 positive, grade 3, Ki67 > 45%)*	5/17: L DCIS Gr 3, central necrosis, BRCA (-), clear margins, clean lymph nodes, Paget's disease of the nipple, ER and PR (-), L mastectomy, no other treatment
Secondary Diagnosis *(ex. Diabetes Type 2, Obesity)*	6/18: metastatic breast cancer to L femur causing fracture with prophylactic fixation of L femur with rod. ER 94%+, PR 47%+, HER2/neu+

Patient Status

☐ New Diagnosis ☐ Recurrence ☐ In Treatment ☐ In Recovery ☑ In Remission ☐ At Risk

Concomitant and/or Complicating Factors *(ex: poorly controlled diabetes, insomnia, poor support system)*	Early insulin resistance Young kids and demanding work
Adverse Effects of Cancer or Cancer Treatments *(ex. anxiety-depression, diarrhea, peripheral neuropathy)*	Peripheral neuropathy in fingers and left toe improved with Accupuncture, pain in elbows
Relevant Laboratory, Pathology & Medical Reports *(attach a PDF with patient identifying information removed or summarize)*	

Brief Summary of Recent History

11/10/18 bilateral salpingo-oophorectomy
11/01/18 normal PET scan
Daily lexapro 10 mg QHS on and off for 10 years
Daily letrozole pill since 11/18 which patient is taking every other day due to SE joint pain
Monthly injections of Xgeva since 7/18
Every 3 week injections of Trastuzumab & Pertuzumab since 7/18

Brief Summary of Additional Relevant Health, Medical, Psycho-Social and/or Family History

Other Relevant Information

Such as Chinese or Ayurvedic diagnosis, Naturopathic/Homeopathic Information, etc. *(ex. Liver Qi Stagnation, Dysbiosis)*

CEA 1.9, CA 27-29 34.1, c reactive protein 5.17, insulin 13.9, vitamin D 60, osteopenia in R femoral neck

Brief Summary of Relevant Past Oncology or Medical Treatments

(ex. surgery, radiotherapy, chemotherapy, immunotherapy, hormone therapy, drug therapy)

5/17: L breast mastectomy
7/18 - 8/10: 12 weeks (once per week) chemo eith Paclitaxel
6/18: prophylactic fixation of L femur with rod
6/18: 15 cycles of radiation to L femur

Summary of Recent and Current Treatments

Medical Oncology Care *(surgery, radiotherapy, chemotherapy, immunotherapy, hormone therapy, drug therapy)*

Integrative Oncology Care *(nutraceutical, botanical, phytochemical, acupuncture, energy medicine, other)*

Acupuncture every 3 weeks
Prayer, meditation, sees dietitian

Your 2 Core Questions (stated clearly and succinctly)

1. How to prevent recurrence of metastatic breast cancer with all available integrative tools while patient is on letrozole?
2. If unable to tolerate letrozole, what is the alternative regimen?

Attached Medical Records for Reference (with patient identifying information removed)

PROPOSED TREATMENT PLAN Your case will not be reviewed without a completed proposed treatment plan

Nutriceutical, Phytochemical and Botanical Supplements (name of supplement, dosing)

Foundation Nutrition Supplements:

DFH OmegAvail Hi-Pro BID
Vital Nutrients CoQ10 200 mg QD
Beta 1,3D Glucan BID empty stomach
DFH B-supreme BID
D3 5,000 QD
Vital Nutrients melatonin 20 mg QHS

Targeted Supplements:

Bosmeric-SR BID
Broccoprotect QD
Ashwagandha QD

Functional Foods and/or Therapeutic Shake

Dietary Guidelines

Low glycemic
Dairy free
Minimal gluten
Vegetarian
Celery juice

Lifestyle Guidelines

Stress management
7-8 hours sleep at night
Prayer, meditation, gratitude

Recommended Diagnostics

Referrals to specialists

Other Notes (please do not include additional notes in your email – notate them here within the case study)

Comments on Monica Sood MD Breast Cancer Case **01.09.19**

Overview: 44 yo Indian American F 142 lbs, insulin resistant, Dx 06/2018 ER+ PR+ her2 neu+ BrCA Metastatic to L femur (post fixation and RT) , post L mastectomy, post CT=Paclitaxel (peripheral neuropathy), post salpingo-oopherectomy, osteopenic R hip, Current tx Letrozole, Trastuzumab, Pertuzumab, Xgeva, lexapro, Current: Normal PET scan, hsCRP 5.17, Vit D 60, normal tumor markers, Acupuncture, meditation, prayer, Sees Dietician

Core Questions:

How to Prevent recurrence?

If unable to tolerate letrozole (joint pain) what is alternative?

Alternatives to Aromatase Inhibitors have been reviewed in prior Grand Rounds Clinical Pearls calls and similar breast cancer case has been previously reviewed in a prior Grand Rounds Call
Please refer to our AIIORE library

Mild Aromatase inhibitors: Chrysin, Resveratrol, Urtica urens root

Support for Bone Health:
Chinese Botanicals
Restore Right Formula (You Gui Tang),
Psoralea, Paenia alba, Fr. Cornii, Epimedium, Rehmannia root (cooked)

Consider Health Concerns OsteoHerbal 2 bid

Need adequate bone mineral supplementation to get full benefit of Denusomab (Xgeva)
Recommend DFH Osteoben 2 bid. (copper free bone health formula)

Encourage increased weight bearing resistance exercise as tolerated (weights, bands, modified yoga, tai chi, pilates,etc/

Need more aggressive anti-tumor support
Early insulin resistance.
Consider Metformin
and/or adding Berberine 1 g tid with meals

CYTOTOXIC
Alternate every other week for one month (do this quarterly=4x/year)
WEEK ONE

Natura PhytoCyto (if possible add extra Taxus brevifolia and Catharanthus rosea)
60 drops tid (diluted, with food)
WEEK TWO
ARG Super Artemesinin 2 tid

Naturopathic Therapies
Oral Low Dose Naltrexone 1.5 titrate up 4.5mg hs
IV C, IV Artesunate, IV Curcumin cytotoxic

IV or SubQ Mistletoe immunotherapy

SAMPLE TREATMENT PLAN

Foundation Nutrients
ITI ProThriver Wellness Multi 1/2x/day. (Cu, Fe, Boron Free)
DFH Vitamin D Supreme 5000iu 2 caps qd
DFH Omegavail TG1000 2/2x/day. 4 grams
DFH Buffered Magnesium Chelate (GLYCINATE) 1/2x/day (use up yours)
KLAIRE Therbiotic Complete (probiotic) 2 caps daily

Targeted Nutrients
Vital Nutrients or Thorne 500mg Berberine 2 tid.
DFH. Curcumevail 2/2x/day 4g
DFH EGCG 2 caps tid 3 g
DFH Broccoprotect 1/2x/day
CS Pure Honokiol 2/2x/day
QOL Labs AHCC 2 bid 3 g
DFH Q Evail 200 mg

Powders
Resvenox 98%Pure Resveratrol 5 g level teaspoon-daily dose

CS Pectasol C Modified Citrus Pectin 5 g 2x/day binds to nutrients away from food (Anti-metastatic)

CS Mycoceutics Mushroom Immune Max Powder (also avail in caps) 2 scoops daily

BEDTIME
VN Melatonin 10-20 mg
DFH Buffered Magnesium Chelate 2 caps
CS Pure Honokiol 2 caps

Sample DAILY Tumor Control Formula with Bone Support Formula and Adaptogens
2 teaspoons daily mixed with warm water or ginger tea
Take with food or shake

240ml	480 ml	
60	120	AntiMastoplasia Formula. (Golden Lotus Herbs)
10	20	Astragalus
10	20	Poria Fu Ling
10	20	Rehmannia
10	20	Epimedium
10	20	Nettle Root extract
15	30	Oldenlandia Heydotis extract
15	30	Scutellaria Huang Qin Extract
15	30	Scutellaria barbata Ban Zhi Lian extract
20	40	Red Sage extract
20	40	Polygonatum
10	20	Ashwanganda Extract
10	20	Green Tea
10	20	Schizandra
5	10	Tangerine Peel

DIET

OutSmart Cancer Diet-Modified Paleo-Keto
Low Carb, Low Sugar, Low Starch, Anti-Inflammatory
Healthy Fats and Oils
Rainbow of colors: vegetables that grow above ground,
Limit fruit to 1 cup berries daily
60 grams+ protein daily
PLATE: 1/2 colorful vegetables, 4 oz protein, healthy fats and oils: olive oil, avocado, humus, almonds, almond butter, walnuts, pine nuts)

Bone Broth 2-4 cups daily (10 grams of protein per cup) Very soothing to lining of digestive tract
Whole Foods or order online from amazon.com or thrivemarket.com
Prefer BonaFideProvisions brand

Intermittent Fasting at least 13-16 hours with no calories increases tumor stress and lowers blood sugar and insulin, promotes ketosis, increases immunity

READING

32 Ways to OutSmart Cancer , Nalini Chilkov OMD

Cancer As a Metabolic Disease by Nasha Winters ND

Anti-Cancer A New Way of Life by David Servan Schreiber.
Read chapter on Low Glycemic Low Carb Diet

Radical Remission, Kelly Turner PhD

REVIEW

Cisplatin-Induced Nephrotoxicity; Protective Supplements and Gender Differences

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Abstract

Cisplatin (CDDP) has been widely used as a chemotherapeutic agent for solid tumors. The most common side effect of CDDP is nephrotoxicity, and many efforts have been made in the laboratory and the clinic to employ candidate adjuvants to CDDP to minimize this adverse influence. Many synthetic and herbal antioxidants as well as trace elements have been investigated for this purpose in recent years and a variety of positive and negative results have been yielded. However, no definitive supplement has so far been proposed to prevent CDDP-induced nephrotoxicity; however, this condition is gender related and the sex hormone estrogen may protect the kidney against CDDP damage. In this review, the results of research related to the effect of different synthetic and herbal antioxidants supplements are presented and discussed with suggestions included for future work.

Keywords: Cisplatin- nephrotoxicity- antioxidant- trace elements- herbal agents- gender

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Introduction

The molecular structure of many therapeutic agents that are used in the clinic contain metals (Chen et al., 2009; Frezza et al., 2010). Cisplatin (CDDP); cis-[PtII(NH3)2Cl2] as an anticancer agent (Frezza et al. 2010; Weiss et al., 1993) is known with the full name of cis-diamminedichloroplatinum(II). (Reedijk et al., 1985). CDDP was synthesized in 1845 and was named as Peyrone's chloride, and later its structure was provided (Alderden et al., 2006; Desoize et al., 2002; Florea et al., 2011; Kauffman et al., 2010). CDDP has undergone several improvements; including transplatin that was first synthesized by Reiset in 1844 (Natile et al., 2001), and finally, the Kurnakow method detected trace quantities of transplatin contaminant (Woollins et al., 1983).

Subsequent experiments made clear the biological effect and inhibition of cell division for platinum (Rosenberg, 1971; Rosenberg et al., 1967; Rosenberg et al., 1965). It was also reported that the cis form of the platinum (IV) complex, [PtCl4(NH3)2], was the agent responsible for inhibition of tumors (Pizarro et al., 2009). Accordingly, platinum (II) complex, cis-[PtCl2 (NH3)2], and platinum (IV) complex, cis-[PtCl4 (NH3)2], were tested against sarcoma tumors in mice, and it was shown to have a remarkable anti-tumor activity and shrinking large solid tumors accompanied with improved mice survival (Rosenberg et al., 1970; Wang et al., 2005). Based on these findings, CDDP as Palatinol® (Bristol-Myers Squibb) became available for clinical practice in 1978 (Florea et al. 2010; Jamieson et al., 1999; Kelland, 2007). The successful results for CDDP in testicular cancer, ovarian and bladder cancers, osteogenic sarcoma, head and neck tumors, endometrial and cervical cancers, and non-small cell lung cancer were documented (Jamieson et al., 1999; Reedijk, 1987; Reedijk et al., 1985). Understanding of drug mechanism is extremely important for a better application of the therapeutic agents in clinic. In this regard, it is clear that CDDP reacts with various cellular components including proteins, DNA, RNA, membrane phospholipids, microfilaments, and thiol-containing molecules (Jamieson et al., 1999; Rebillard et al., 2008; Speelmans et al., 1996; Speelmans et al., 1997). CDDP maintains a relatively stable neutral state in blood (Alderden et al., 2006; Jamieson et al., 1999; Jung, 2005; Reedijk, 1987; Reedijk et al., 1985) and binds to blood proteins while this binding is hampered by high concentration of chloride in blood; so one day after CDDP administration, 65–98% of the platinum in blood is protein-bound (Alderden et al., 2006; Barnham et al., 1996; Ivanov et al., 1998; Keppler,

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1993). The CDDP component that remains intact can enter tumor cells (Mellish et al., 1994; Wiltshaw, 1979). In addition, due to the lower chloride concentration inside the cell, chloride ions are replaced with water molecules, and this platinum compounds; cis-[Pt (NH3)2(H20) CI]+ is an active form of CDDP bound to DNA (Alderden et al., 2006; Chu, 1994; Jamieson et al., 1999; Jung, 2005; Reedijk, 1987; Reedijk et al., 1985). Generally, it is accepted that cell death occurs due to inhibition of DNA synthesis (S phase arrest) (Harder et al., 1970; Howle et al., 1970; Jamieson et al., 1999; Salles et al., 1983; Weiss et al., 1993). However, some studies indicated that cells treated with CDDP progressed through the S phase, where DNA synthesis occurs, and were arrested in the G2 phase (Sorenson et al., 1988a; Sorenson et al., 1988b). Finally, the analysis of apoptosis induced by CDDP reveals DNA fragmentation followed by loss of membrane integrity and cell shrinkage (Sorenson et al., 1990).

Renin angiotensin system (RAS) and CDDP-induced nephrotoxicity

The renin angiotensin system (RAS) has been involved in the pathogenesis of kidney diseases and drug-induced nephrotoxicity. CDDP-induced acute renal failure in rats indicates structural alteration in the renal tubular epithelia, which is associated with changes of renal functions. CDDP alters renal hemodynamics (Hye Khan et al., 2007), attenuates glomerular filtration rate (GFR) and renal blood flow (RBF), and increases plasma renin activity and renal vascular resistance (RVR); this is while it does not affect mean arterial pressure (MAP) (Cornelison et al., 1993; Hutchison et al., 1988; Hye Khan et al., 2007; Matsushima et al., 1998; Winston et al., 1985). Hemodynamic changes may be related to RVR induced by tubular-glomerular feedback (Cornelison et al., 1993). RAS receptors may also involve in CDDP-induced nephrotoxicity, and in this regard, it is reported that angiotensin type 1 receptor (AT1R) blocker protects the kidney against CDDP in male rats (Haghighi et al., 2012).

Immediately after CDDP administration, although RBF and GFR do not undergo alterations, the rate of proximal reabsorption decreased significantly; so destructive effect of CDDP initiates from proximal tubule before changes in renal hemodynamics occur (Daugaard, 1990; Daugaard et al., 1989). CDDP also decreases sodium transporters including Na-K-ATPase and Na-K-2CL co-transporters and Na-H exchanger (Daugaard et al., 1989). The effect of CDDP on sodium and water transport represents an early change in kidney to induce tissue toxicity (Daugaard et al., 1989; Lajer et al., 2005a). CDDP also causes abnormities in the renin-aldosterone system (Bosl et al., 1986; Iida et al., 2000). Treatment with CDDP reduces mineralocorticoid receptor binding (Iida et al., 2000) as the genes for amiloride-sensitive epithelial sodium channel and Na-k-ATPase are regulated by aldosterone positively (Masilamani et al., 1999; Wang et al., 1994).

Plasma levels of aldosterone and angiotensin II increase after CDDP therapy (Okui et al., 2012) whereas administration of angiotensin converting enzyme (ACE) inhibitor and AT1R blockers fails to reduce the elevation of plasma aldosterone level induced by CDDP (Okui et al., 2012). This finding suggested that ACE-mediated AngII/AT1R signaling system may not be involved in acute renal failure induced by CDDP (Daemen et al., 1999). ACE inhibitors either synthetic such as captopril or herbal have protective effects against CDDP-induced nephrotoxicity. Another group of ACE inhibitors is flavonoids that can improve renal function in CDDP-treated rats (Balasuriya et al., 2011). Losartan is an AT1R blocker and antioxidant agent, and it has been the target of treatment to protect against CDDP-induced nephrotoxicity (Saleh et al., 2009) while different responses have been reported in acute or chronic administration of AT1R blocker (Deegan et al., 1995; Haghighi et al., 2012). It is accepted that CDDP may disturb renal hemodynamics parameters including RAS; however, the induced nephrotoxicity is not due to hemodynamics disturbance alone. AT1R blocker or ACE inhibitors may attenuate renal toxicity in CDDP therapy, but it is hard to accept these agents as the optimal protective agents against CDDP-induced nephrotoxicity.

Synthetic antioxidants supplementation on CDDP-induced nephrotoxicity

Vitamins C and E are essential nutrients that act as non-enzymatic factors in cytosol and membrane cells. These vitamins have protective role against CDDP-induced nephrotoxicity (Ajith et al., 2009; Ajith et al., 2007). Vitamin C is involved in many biological processes, and acts as a protective agent against neoplasms and the damage involved in oxidative stress (Greggi Antunes et al., 2000) and renal glutathione (GSH) depletion (Meister, 1992). Under conditions such as low iron level, low concentration of vitamin C causes lipid peroxidation (Halliwell B, 1989). Vitamin C also inhibits glomerular damages by preventing production of free radicals (Appenroth et al., 1997).

Vitamin E as an antioxidant and membrane stabilizer has protective effect against CDDP-induced nephrotoxicity (Fang et al., 2002; Wang et al., 1999) while CDDP decreases vitamin E in kidney tissue (Nazıroğlu et al., 2004). Ajith et al. have shown that the use of CDDP increases serum creatinine (Cr) and blood urea nitrogen (BUN) levels while supplementation of vitamins C and E reduces serum Cr and BUN levels (Ajith et al., 2007). Administration of a single dose of vitamins C, E and combination of vitamins C and E decrease the serum level of malondialdehyde (MDA) after CDDP treatment (Ajith et al., 2009). Twenty four hours after CDDP administration, 55% increase in GSH concentration was detected while vitamin C induced a slight decrease in GSH (Greggi Antunes et al., 2000). Naziroglu et al. showed that administration of CDDP increases MDA and decreases GSH peroxidase (GSH-Px) levels in serum (Nazıroğlu et al., 2004).

The glycoside derivatives of vitamin C are more stable, and are able to act as free radicals scavengers (Fujinami et al., 2001) and antioxidant agents (Mathew et al., 2007), which reduce DNA lipid membrane injuries (Claycombe et al., 2001). Monoglycoside tocophrol is a water-soluble derivative (Kapoor et al., 2002) and its combination with vitamin C could prevent the CDDP-induced antioxidant depletion (Maliakel et al., 2008). It is also suggested that

pretreatment with vitamin E compensates CDDP-induced nephrotoxicity, and this effect is not enhanced by a second vitamin E administration, while simultaneous administration of vitamin C and E twelve hours prior to CDDP intensifies the protective effect of vitamin E (Appenroth et al., 1997). GSH has protective effect against CDDP nephrotoxicity, and its depletion leads to lipid peroxidation; so treatment with vitamins C and E improves GSH concentration and enhances protection against CDDP side effects (Abraham, 2005; Babu et al., 1995). This is while decrease in GSH concentration leads to enhance susceptibility to chemical damage and oxidative stress, because GSH as a non-protein thiol plays an important role in formation of the metabolite drug conjugate compounds (Rana et al., 2002). CDDP causes a reduction of 64% in zinc (Zn) and 55% in copper (Cu) content of cytosol, and decreases superoxide dismutase (SOD) activity. This activity is related to reduced content of Cu and Zn as essential elements for SOD activity (Sharma, 1985).

AT1R blockers such as losartan also act as an antioxidant. Actually, losartan acts via inhibiting vasoconstriction and increasing renal blood flow (Ullman et al., 2001a; Ullman et al., 2001b). It is reported that co-administration of vitamin C and losartan do not have protective effect for kidney tissue; in contrast to losartan alone that shows protective effect. Co-administration of vitamin C and losartan may lead to drug interaction that limits the effectiveness of losartan (Ashrafi et al., 2012b). Similarly, co-administration of losartan and vitamin E do not protect against CDDP-induced nephrotoxicity (Nematbakhsh et al 2012a) while estradiol may abolish the losartan effect against CDDP-induced nephrotoxicity (Ghadirian et al., 2015).

Erythropoietin (EPO) is another antioxidant studied in this regard. It belongs to the large family of cytokine-1. Hypoxia releases EPO from fibroblast-like cells in the cortex of the kidney (Jacobson et al., 1957). EPO initially was identified as a glycoprotein hormone produced mainly in the liver and kidney (Fisher, 2003). It is more than 30 years that kidney is recognized as the primary site of EPO production (Jacobson et al., 1957) and bone marrow as its target organ (Nagai et al., 1995b). EPO also has anti-apoptotic (Bartesaghi et al., 2005; Mohamed et al., 2013), antioxidant (Katavetin et al., 2007), and anti-inflammatory (Marti, 2004; Mohamed et al., 2013) activities. EPO has been used as a nephroprotective against various kidney injuries such as kidney damage induced by ischemia-reperfusion (Sharples et al., 2004; Vesey et al., 2004), CDDP-induced nephrotoxicity (Bagnis et al., 2001; Kong et al., 2013; Rjiba-Touati et al., 2011; Yalcin et al., 2003; Zafirov et al., 2008), and gentamicin-induced kidney toxicity (Rafieian-Kopaei et al., 2012). The results obtained by Zafirov et al. showed that increase in BUN and Cr as well as proteinuria induced by CDDP are improved after EPO administration, and they suggested that recombinant human EPO significantly reduces renal failure and renal damage induced by CDDP (Zafirov et al., 2008). In a study, it was reported that RBF and GFR significantly reduced on the fourth day after CDDP administration while on the ninth day after EPO administration, both RBF and GFR increased, and tubular cell regeneration on the fourth day after EPO injection enhanced significantly (Bagnis et al., 2001). EPO administration reduces the serum level of Cr induced by CDDP; and also cell death induced by CDDP terminated by EPO. In addition, EPO suppresses the increased expression of endoplasmic reticulum stress markers (CHOP and GRP78) and attenuates the suppression of phosphatidylinositol-3kinase/akt signaling induced by CDDP (Kong et al., 2013). Based on our laboratory data, EPO improved CDDP-induced nephrotoxicity while female sex hormones inhibits this effect (Pezeshki et al., 2012).

A study has shown that administration of EPO in animals treated with CDDP improves GSH level and decreases MDA level in the serum while increased expression of inducible nitric oxide (NO) synthase (iNOS) and serum nitrite level are attenuated by EPO (Mohamed et al., 2013). EPO by several mechanisms including reduction of oxidative and nitrosative stress, decreased expression of vascular endothelial growth factor (VEGF), and improvement of Bc12 immunoreactions in tubular cell can improve renal function (Mohamed et al., 2013).

Alpha lipoic acid (ALA), a necessary cofactor for mitochondrial enzymes, is introduced as a new antioxidant and acts as free radical scavenger (Biewenga et al., 1997; Packer et al., 1995). This agent is used for neurodegenerative disorders, heavy metal toxicity, and oxidative tissue injury (Nagamatsu et al., 1995; Panigrahi et al., 1996). It also has therapeutic effects on diabetes, polyneuropathy, cataract, neurodegeneration, and nephropathies (Alegre et al., 2010; Amudha et al., 2007). It serves similar to lipoamid as a cofactor in the multi-enzyme system for catalysis of oxidative decarboxylation of α-keto acids (Marangon et al., 1999). ALA chelates platinum and prevents its accumulation in renal tissue in CDDP-induced nephrotoxicity (Nagamatsu et al., 1995; Panigrahi et al., 1996). Somani et al. have reported that increased Cr level induced by CDDP is improved after administration of graded doses of ALA (12, 50, 100 mg/kg) (Somani et al., 2000). Furthermore, CDDP administration reduces GSH, GSH-Px, and GSH-reductase; which increase after treatment with different doses of ALA (50, 100 mg/kg), decreases SOD activation, and increases MDA concentration that is corrected by ALA (Somani et al., 2000). ALA is a thiol containing nucleophile that reacts with free radicals and heavy metals. Thereby, it might act as scavenger of reactive oxygen species free radicals, chelator of platinum in renal tissue that inhibits lipid peroxidation, and increases glutamine (Somani et al., 2000). Treatment of mice with CDDP elevates MDA level and decreases GSH while ALA administration decreases MDA and increases GSH levels. In addition, CDDP treatment leads to decline in catalase, SOD, and GSH-Px activities, all of which improve after ALA administration. ALA also ameliorates oxidative stress and enhances gene expression of antioxidant enzymes (El-Beshbishy et al., 2011). Moreover, ALA reduces the depletion of GSH level in the kidney of rats treated with CDDP and provides nephroprotection (Mistry et al., 1991; Somani et al., 1995). The recovery of renal SOD, catalase, GSH-Px, and GSH

reductase with lipoic acid pretreatment suggests that this factor can protect these enzymes three days after CDDP administration (Mistry et al., 1991; Somani et al., 1995).

N-acetylcysteine (NAC) is a thiol-containing antioxidant, which was originally introduced as a mucolytic drug (Dickey et al., 2005a; Mishima et al., 2006). The results have shown that NAC is able to inhibit activation of P38 mitogen-activated protein kinases (p38MAPK), biosynthesis of tumor necrosis factor alfa (TNF-α), and activation of nuclear factor-κB (NF-κB) (Li YQ, 2006). It is also able to inhibit CDDP-induced apoptosis and it is shown to be the precursor of GSH (Wu et al., 2005). NAC is the compensator for cellular GSH resources and also acts as scavenger of oxygen free radicals (Nisar et al., 2002). The effect of NAC is due to a direct effect of the drug (e.g., inactivation of hydroxyl radicals) or it is related to induction of GSH production (Fishbane et al., 2004). Previous studies have shown that NAC improves CDDP nephrotoxicity in humans and rats (Appenroth et al., 1993; Dickey et al., 2008; Dickey et al., 2005a; Somani et al., 2000). It should be considered that the route of NAC administration is important in protection of CDDP nephrotoxicity; for instance, intravenous infusion leads to better results in comparison with oral or intraperitoneal administration (Dickey et al., 2008). In a case study, Hanad et al. have reported that in 52-year-old female who developed acute renal failure after administration of 150 mg CDDP for treatment of squamous cell cancer of the esophagus, the serum levels of BUN and Cr increased from 12 and 0.7 mg/dL to 24 and 1.8 mg/dL, respectively, on day 5 after CDDP administration. She was subjected to treate with NAC (140-mg/kg-body weight followed by 70 mg/kg every 4 h for 4 days), and two days later, renal function began to improve, and after 10 days, her serum Cr reduced to 0.8 mg/dL (Nisar et al., 2002). Another study indicated that NAC may reverse CDDP-induced nephrotoxicity (Sheikh-Hamad et al., 1997). NAC (500 mg kg-1 per day for 9 days) restored the renal hemodynamics, as well as the biochemical and histopathological changes induced by CDDP (Abdelrahman et al., 2010). Luo et al. have demonstrated that NAC suppresses oxidative stress, p38 MAPK activation, caspase-3 cleavage, tissue apoptosis, renal dysfunction, and morphological damage induced by CDDP. They suggested that at least in part, oxidative stress and cell death pathways related to p38 MAPK are involved in the pathogenesis of CDDP-induced acute renal failure (ARF) (Luo et al., 2008). It seems that inhibition of p38 MAPK activity inhibits oxidative stress and therefore improves renal function.

Deferoxamine (DFX) is a natural trihydroxamate that has antioxidant properties (Freedman et al., 1989). Possibly its antioxidant property is independent of its capability to bind iron (Shimoni et al., 1994). It is an iron chelator and is used to treat iron overload (Maxwell, 1995). It has been reported to be useful in treatment of Alzheimer's (Cuajungco et al., 1998), stroke (Hurn et al., 1995), encephalomyelitis (Bowern et al., 1984), acute renal failure (Paller et al., 1988; Shah et al., 1988; Walker et al., 1988), and CDDP-induced nephrotoxicity (Baliga et al., 1998a). Iron plays an important role in tissue damage caused by oxidative stress (Halliwell et al., 1989). Increased iron level catalyzes free radical reactions involved in ischemia/reperfusion-induced acute renal failure (Baliga et al., 1993), glycerol-induced acute renal failure (Baliga et al., 1996), and CDDP-induced nephrotoxicity (Baliga et al., 1998a). Iron chelators, including DFX and 2,3-dihydroxybenzoic acid, have protective effect in several models of acute renal failure (Paller et al., 1988; Shah et al., 1988; Walker et al., 1988) and oxidant-induced damage (Paller et al., 1991; Walker et al., 1991) including CDDP nephrotoxicity. Similarly, CDDP-induced acute renal failure is improved by DFX administration in rats (Baliga et al., 1998a). It is nice to know that hydroxyl radical scavengers, dimethyl sulfoxide, mannitol, and benzoic acid significantly decrease CDDP-induced toxicity; and treatment with dimethyl sulfoxide or dimethylthiourea causes significant protection against CDDP-induced ARF; taken together, these data support critical role of iron in mediating tissue injury via hydroxyl radical in this model of nephrotoxicity (Baliga et al., 1998a). DFX pretreatment reduces renal dysfunction and lipid peroxidation induced by CDDP; while at the same time increases non-protein sulfhydryl (-SH) concentrations in the kidney tissue (Özdemir et al., 2002), which involved ROS system (Guelman et al., 2004).

Glutamine is one of the most abundant amino acids in the body (Bergstrom et al., 1974). One of its most important roles is to participate in the metabolism of GSH (Wu et al., 2004). GSH is a potent antioxidant and plays an important role in the metabolism of exogenous and endogenous substances (Wu et al., 2004). GSH participates in many cellular reactions. It directly scavenges free radicals and other reactive oxygen species (hydroxyl radical, lipid peroxyl radical, peroxynitrite, and H2O2), and is indirectly related to enzymatic reactions (Fang et al., 2002). Mora et al. have reported that CDDP injection increases renal GSH level (Mora et al., 2003), and the level returned to normal by glutamine administration. In addition, 24 hours after glutamine administration, the increased lipid peroxidation induced by CDDP came back to the normal level; however, glutamine does not inhibit the increase in renal GSH 7 days after treatment (Mora et al., 2003). Salicylates are anti-inflammatory, analgesic, antipyretic and antithrombotic agents. Aspirin is the most common form that is metabolized in the serum within 15 to 30 minutes, and its anti-inflammatory effect is related to inhibition of cyclohexane-oxygenase 2 (Chernov et al., 1997). Aspirin also acts as hydroxyl radical scavenger (Ghiselli et al., 1992). Li G et al. have demonstrated that administration of salicylate reduces BUN and serum Cr levels induced by CDDP (Li et al., 2002). It seems that antioxidant agents, in general have some protective effect against CDDP-induced nephrotoxicity. However, selection of the most appropriate antioxidant supplement is of great importance. Fighting the CDDP-induced oxidative stress via antioxidants is only one side of the coin, while special attention should be paid to the other side of the coin including renal hemodynamics and kidney processes and reduction of CDDP effect on target tumor. In addition, it should be mentioned that

some others protective approaches against CDDP induced nephrotoxicity like oxygen pretreatment have been studied by others (Rasoulian et al., 2010; Kaeidi et al., 2013; Rasoulian et al., 2014; Saadat et al., 2014;).

Mineral elements and CDDP-induced nephrotoxicity

Mineral elements such as magnesium (Mg), Zn, Cu, sodium (Na), and selenium (Se) are necessary in biological and physiological processes (Bray et al., 1990; Fawcett et al., 1999; Rayman, 2000; Soetan et al., 2010). Mg as the most common cation in the body plays an essential role in enzymatic reactions (Fawcett et al., 1999). Advantages of Mg supplementation in diabetes (Soltani et al., 2005) and endothelial function (Barbagallo et al., 2010) have been documented. Hypomagnesaemia is one of the most important disturbances in cancer patients (Anvari et al., 2010; Arunkumar et al., 2011; Hodgkinson et al., 2006; Lajer et al., 2005b; Stewart et al., 1985; Zumkley et al., 1982). In addition, hypomagnesaemia may induce hypocalcaemia (Lyman et al., 1980) via three mechanisms of inhibiting parathyroid hormone secretion, reducing responses of tissue to parathyroid hormone (Anast et al., 1976; Estep et al., 1969), and impairing the release of calcium from bone (Johannesson et al.,1983 et al., 1983). Clinical studies indicate that Mg supplements could ameliorate CDDP-induced nephrotoxicity (Anvari et al., 2010; Hirai et al., 2013; Hodgkinson et al., 2006; Kidera et al., 2014; Muraki et al., 2012; Wcislo et al., 2008; Willox et al., 1986; Yoshida et al., 2014). Recently, experimental studies have shown that administration of Mg supplementation did not reduce CDDP-induced nephrotoxicity, rather intensified it. Ashrafi et al., (2012a) examined intraperitoneal administration of various doses of Mg sulphate (20, 80, and 200 mg/kg) against CDDP-induced nephrotoxicity in rat model. Noteworthy the low dose of Mg supplementation aggravated renal dysfunction, while high doses of Mg sulphate did not protect the kidney against CDDP. In addition, Soltani et al., (2013) demonstrated that oral administration of Mg sulphate (10 g/l) exacerbated nephrotoxicity in diabetic and normoglycemic rats (Soltani et al., 2005). There is a correlation between Mg level and OCT2, and up-regulation of OCT2 in Mg-deficient diet enhances renal accumulation of CDDP (Yokoo et al., 2009). In another study mice were exposed to Mg-deficient diets for two weeks, and after CDDP administration, the animals received 0.3% MgCl2 and MgSO4 (100 mg/kg/day) through drinking water and subcutaneous injection, respectively, and Mg supplementation ameliorated renal failure and apoptosis induced by CDDP (Solanki et al., 2014). Oral administration of Mg sulphate (3 and 10 g/l) alone do not protect the kidney against CDDP-induced nephrotoxicity while the combination of AT1R blocker; losartan and Mg sulphate (3 g/l) ameliorate the nephrotoxicity induced (Razmjoo et al., 2014). Some studies, however, have shown positive effects of various doses of Mg (0.6% in diet, 2% and 0.6% in drinking water) on renal failure induced by cyclosporine (Asai et al., 2002; Burdmann et al., 1994; Kimura, 2000; Mervaala et al., 1997; Pere et al., 2000; Yuan et al., 2005). The combination of Mg supplementations with potassium (Pere et al., 2000) or NAC (de Araujo et al., 2005; Malek, 2013) are efficient to attenuate renal function against various failure models in the kidney.

Se is another necessary element which participates in biological processes (Rayman, 2000). A clinical study showed cancerous patients under CDDP chemotherapy that received Se supplementation did not exhibit ARF (Ghorbani et al., 2013), while similar results were reported by Hu et al. study (Hu et al., 1997). Francescato et al. administered Se (2 mg/kg, by gavage) 24 h and 1 h prior to administration of CDDP and continued for the next seven days. They observed that Se treatment ameliorated serum level of Cr and renal level of MDA as well as kidney damage, but not other parameters such as renal GSH and Cr clearance (Francescato et al., 2001). Se reduces nephrotoxicity induced by CDDP (Baldew et al., 1988; Berry et al., 1984) without direct effect on tumor cells or antitumor activity of CDDP (Berry et al., 1984). In addition, depletion of Se itself induces oxidative stress, which results in progression of CDDP-induced nephrotoxicity (Araya, 1990; Fujieda et al., 2006). This is while Se treatment decreases such renal damage (Araya, 1990; Fujieda et al., 2006) with no effect on blood cells and liver (Araya, 1990; Araya et al., 1990). Baldew et al. examined the effect of sodium selenite (2 mg/kg) before and after CDDP administration and suggested protective effect of Se on nephrotoxicity when it was administered before CDDP (Baldew et al., 1989). They also concluded that selenite protect kidney against CDDP toxicity through reaction of selenite metabolite with CDDP in the presence of GSH without reducing CDDP antitumor activity (Baldew et al., 1991). The combination of Se with a high dose of vitamin E also improves antioxidant state in CDDP-induced nephrotoxicity animal model (Naziroglu et al., 2004). This was confirmed by Hemati et al. in a clinical study (Hemati et al., 2012). In contrast with previous reports, it was demonstrated that Se orally has no protective effect against nephrotoxicity induced by CDDP (Antunes et al., 2001). Also, oral single dose of Se could ameliorate proximal tubular injury, but not renal dysfunction (Camargo et al., 2001). In another study, Se nanoparticles inhibited generation of ROS induced by CDDP in cell culture and blocked apoptosis in a dose-dependent manner (Li et al., 2011). Different supplementation regimens of Se ameliorate renal toxicity induced by CDDP and decrease mortality rate (Naganuma et al., 1984; Naganuma et al., 1983; Satoh et al., 1992; Satoh et al., 1989; Vermeulen et al., 1993; Yokoyama et al., 1985; Zhang et al., 2008a). Pretreatment with Se could inhibit CDDP-induced kidney and liver damage (Imaga et al., 2014). Furthermore, short-term administration of sodium selenosulfate reduces gastrointestinal disturbances induced by CDDP while long-term administration of sodium selenosulfate is more efficient in reducing side effects of CDDP in comparison with sodium selenite (Li et al., 2012).

Daley-Yates et al., (1985) examined the effect of chloride salts on nephrotoxicity induced by CDDP, and reported that administration of sodium chloride (NaC1) or NH4C1 90 min before CDDP could prevent nephrotoxicity in rats, although NaC1 had no protective effect when

given 3 or 24 hr after CDDP administration. Another study showed that NaCl loading has lower protective effect than acetazolamide, although it decreases the rate of mortality induced by CDDP (Heidemann et al., 1990). The patients who received sodium loading alone or sodium loading with forced diuresis showed no difference in incidence of nephrotoxicity induced by CDDP (Leu et al., 2010).

Sodium thiosulfate (ST) suppresses the nephrotoxicity induced by CDDP in human gastric cancer transplanted in nude mice, although reduces antitumor effect of CDDP (Saito et al., 1989; Wagner et al., 1988). Therefore, it is suggested to use low dose of ST in CDDP chemotherapy (Fujii et al., 1988). Intraperitoneal or intravenous injections of ST attenuate the CDDP-induced hypomagnesemia and nephrotoxicity (Wong et al., 1988). ST is also known as effective agent to decrease level of total kidney platinum (Nagai et al., 1995a), and administration of ST increases antitumor effects of CDDP in bladder tumor (Sagiyama et al., 1983), while it also decreases nephrotoxicity in the patients treated with CDDP (Vance et al., 1986). In a clinical trial, simultaneous administration of ST and CDDP permits higher dose of CDDP (at least two folds) in patients under chemotherapy (Pfeifle et al., 1985) without raising the Cr level (Howell et al., 1982). In addition, ST protection increases survival in guinea pigs treated by CDDP and could enhance animal tolerance against doses three times higher than the toxic dose of CDDP (Leitao et al., 2003). It should be emphasized that the time of ST administration is very important to exhibit anti-cytotoxic and anti-apoptotic effects against CDDP (Dickey et al., 2005b). ST is found to block CDDP-induced nephrotoxicity, although platinum concentration in subcellular fractions indicates that ST cannot fully protect against nephrotoxicity (Uozumi et al., 1986). Different routes of sodium malate administration; e.g., intravenous, intraperitoneal, subcutaneous, and oral are shown to reduce nephrotoxicity induced by CDDP through binding to CDDP and converting into diammino-platinum (II) malate (Ueda et al., 1998a; Ueda et al., 1998b).

Zn has protective and antioxidant effects (Bray et al., 1990). Zn sulphate pretreatment is shown to increase survival in CDDP-induced nephrotoxicity and reduce iNOS activity (Joshi et al., 2004). Also, Zn supplementation could ameliorate nephrotoxicity induced by CDDP through preventing lipid peroxidation (Huang et al., 1997; Srivastava et al., 1995; Tuzcu et al., 2010) and inflammation (Tuzcu et al., 2010).

Máthé et al., (2013) reported that chronic administration of CV247 (an aqueous mixture of Cu gluconate, manganese (Mn) gluconate, vitamin C, and sodium salicylate) can reduce renal histological damage induced by CDDP through decreasing reactive oxidants, but it does not prevent increasing the levels of BUN and Cr. Another study has shown that metalloporphyrins such as iron(III) tetrakis (N-methyl-4'-pyridyl) porphyrin (FeTMPyP) and Mn(III) tetrakis (4-benzoic acid) porphyrin (MnTBAP) as peroxynitrite scavengers attenuate nephrotoxicity induced by CDDP via decreasing DNA fragmentation, apoptosis and nitrative stress, and this protection effect is observed 12 h after CDDP administration (Pan et al., 2014). An in vivo study reported that, combination of iron and aminolevulinic acid (a precursor of tetrapyrrole compounds) can prevent mitochondrial structural changes and ameliorate decreasing in mitochondrial enzymes, while it decreases apoptosis and increases heme concentration in CDDP toxicity (Terada et al., 2013). However, in vivo and in vitro studies indicate that CDDP increases catalytic iron that results in elevating BUN and Cr levels (Baliga et al., 1998a; Baliga et al., 1998b) and iron chelators ameliorate renal dysfunction (Baliga et al., 1998a; Özdemir et al., 2002). Accordingly, it is clear that CDDP therapy disturbs the levels of some trace elements; however, the correlation between CDDP-induced nephrotoxicity and disturbance of a specific trace element is not completely known. Therefore, it is hard to suggest a specific trace element as a supplement to fully protect the kidney against CDDP-induced toxicity.

Diseases and CDDP-induced nephrotoxicity

In clinic, patients that undergo chemotherapy may suffer from other medical conditions such as hypertension, ischemic heart disease and diabetes mellitus (Mathe et al., 2011). Here, a question is proposed "Could the diseases affect nephrotoxicity induced by CDDP?" A study showed that nephrotoxicity is aggravated by diabetes mellitus plus ischemic heart disease in lung cancer patients (Mathe et al., 2011). In another study, it is reported that nephrotoxicity develops similarly in diabetic and non-diabetic patients treated by CDDP (Weese et al., 2009). Animal experiments have shown that diabetic kidney is resistance against CDDP-induced nephrotoxicity (Sarangarajan et al., 2004; Sarangarajan et al., 1996; Sarangarajan et al., 1999; Scott et al., 1989; Scott et al., 1990; Valentovic et al., 1991), and administration of insulin reverses this protection (Sarangarajan et al., 2004) but normalization of high glucose in diabetic animal model by oral vanadyl sulphate have no effect on diabetes-induced protection against CDDP nephrotoxicity (Sarangarajan et al., 1999). Various mechanisms have been proposed to be responsible for protection induced by diabetes against CDDP in rats. Firstly, urinary platinum excretion is greater in diabetic group than that in non-diabetic group for 48 h after CDDP injection (Valentovic et al., 1991). Secondly, diuresis induced by high levels of glucose is not responsible for attenuation of nephrotoxicity in diabetic model (Scott et al., 1990). Thirdly, diabetic state decreases renal platinum accumulation (Cacini et al., 1991; Sarangarajan et al., 1997; Sarangarajan et al., 2004). OCT2 system is responsible for transportation of CDDP into the proximal tubule cells, and this system is impaired in the kidneys of streptozotocin (STZ)-diabetic rats (Grover et al., 2002) and this in turn disturbs renal platinum accumulation in the diabetic kidneys (Sarangarajan et al., 1997). However, diabetes has no protective effect in patients against CDDP-induced nephrotoxicity. The involved mechanisms are not known and further investigations are required to determine the underlying cause. In this regard, Mathe et al., (2011) reported that both hypertension plus ischemic heart disease and diabetes mellitus plus ischemic heart disease predispose lung cancer patients to nephrotoxicity induced by CDDP.

Herbal agents in CDDP-induced nephrotoxicity

Today, herbal medicine provides an opportunity for treatment of some diseases and prevention of abnormal side effects induced by synthetic drugs (Sohn et al., 2009). Patients who are not satisfied with chemical medicine may focus on herbal medicine. Different studies have documented antioxidant effect of herbal agents (Ekor et al., 2010; Elmhdwi, 2013; Gulec et al., 2006; Hadjzadeh et al., 2013; Sohn et al., 2009); so, many researches have been performed to determine the role of herbal medicine in CDDP-induced nephrotoxicity (Table 1).

Oxidative stress in renal tubules is caused by different free oxygen radicals such as superoxide anion, hydrogen peroxide, and hydroxyl radicals (Baek et al., 2003). It seems that phenolic components, especially flavonoids, are powerful sources of antioxidant. This is while many plants contain flavonoids, and these components exert protective effect against CDDP-induced nephrotoxicity (Karimi et al., 2005; Öztürk et al., 2007). Silymarin has a mixture of three flavonolignans that can scavenge free radicals and increase GSH level (DerMarderosian et al., 2002; Thomas, 2000). Ginkgo biloba is a source of flavonoids and considering its quercetin content is considered as an antioxidant herb (Inselmann et al., 1995; Song et al., 2013; Trompezinski et al., 2010).

Carob and Morus alba L. leaves are rich in flavonoids (Elmhdwi, 2013; Nematbakhsh et al., 2013b). Other studies have shown that grape seed proanthocyanidin extract (GSPE) has antioxidant effect that could downregulate oxidative stress proteins, while its antioxidant effect is 50 times higher than vitamin E and 20 times that of vitamin C (Chacón et al., 2009; Gao et al., 2014; Li et al., 2008; Terra et al., 2009). Lipid peroxidation caused by oxidative stress and thiobarbituric acid reactive substances (TBARS) is the final product of lipid peroxidation that increases when CDDP is administrated (Karthikeyan et al., 2007; Saad et al., 2009). Free radicals exert wide tissue damage due to their reaction with macromolecules such as membrane lipids, proteins, and nucleic acids (Conklin et al., 2008; Satoh et al., 2003). GSH is one of the critical compounds to maintain cell integrity, regulate cell function, and protect cells from oxidative stress and free radicals. It is shown that thiol portion of GSH reacts with alkylating agents such as CDDP (Atessahin et al., 2005), and CDDP decreases the level of GSH in the kidneys (Yilmaz et al., 2004). Other antioxidant enzymes are GSH S-transferase (GST) and GSH peroxidase (GSH-Px) that are GSH-depended antioxidant enzymes (Karthikeyan et al., 2007). GSH-Px is an essential endogenous antioxidant enzyme that can delete hydrogen peroxide and lipid

Table 1. Different Effects of Some Herbal Extracts in Different Studies on CDDP-Induced Nephrotoxicity Models

Herbal extract	Observation
Paeonia suffruticosa (Sohn et al., 2009)	Decreasing cytotoxic and genotoxic effects
Curcumal longa (Sohn et al., 2009)	Decreasing cytotoxic and genotoxic effects
Centipeda minima (Sohn et al., 2009)	Decreasing cytotoxic and genotoxic effects
Loranthus parasiticus (Sohn et al., 2009)	Decreasing cytotoxic and genotoxic effects
Pulsatilla dahurica (Sohn et al., 2009)	Decreasing cytotoxic and genotoxic effects
Sinapis alba (Sohn et al., 2009)	Decreasing cytotoxic and genotoxic effects
Scutellaria barbata (Sohn et al., 2009)	Decreasing cytotoxic and genotoxic effects
Rheum ribes (Hadjzadeh et al., 2013)	Decreasing BUN, No effect on Cr and kidney tissue damage score (KTDS)
Milk thistle (Karimi et al., 2005)	Decreasing BUN, Cr, and KTDS
Grape seed (GSPE) proanthocyanidin extract (Gao et al., 2014; Saad et al., 2009)	Decreasing BUN, Cr, apoptosis, inflammatory and oxidative stress, and DNA degradation
Polyphenolic extract of soybean (PESB) (Ekor et al., 2010)	Decreasing BUN, Cr, KTDS, and oxidative stress
Rubia cordifolia (RCE) (Joy et al., 2008)	Decreasing BUN, Cr, oxidative stress and MDA
Ginkgo biloba (Song et al., 2013)	Decreasing KTDS, BUN, Cr, oxidative stress
Curcuma comosa (Jariyawat et al., 2009)	Decreasing BUN, Cr, oxidative stress
Morchella esculenta (Nitha et al., 2008)	Decreasing BUN, Cr, oxidative stress
Ceratonia siliqua L. (Elmhdwi, 2013)	Decreasing BUN, Cr, MDA, oxidative stress
Pomegranate flower (Motamedi et al., 2014)	Decreasing BUN, Cr, KTDS
Fennel essential oil (Mazaheri et al., 2013)	No effect on BUN, Cr, MDA and KTDS
Morus alba (Nematbakhsh et al., 2013b)	Decreasing BUN, Cr, KTDS
Prunus persica flesh (Lee et al., 2009)	Decreasing BUN, Cr and oxidative stress
Brassica rapa (Kim et al., 2006)	Decreasing MDA, oxidative stress, BUN, Cr, and urinary LDH
Leea asiatica (Sen et al., 2013)	Decreasing BUN, Cr, Uric acid, and MDA
Pueraria tuberosa (Nagwani et al., 2010)	Decreasing BUN, Cr, oxidative stress, KTDS
Lagerstroemia speciosa (Priya et al., 2007)	Decreasing BUN, Cr, oxidative stress
Ginger extract (Ali et al., 2013)	Decreasing BUN, Cr, KTDS, and apoptosis
Phellinus rimosus (Ajith et al., 2002)	Decreasing oxidative stress

peroxide and protect cellular membrane from peroxidative damages (Karthikeyan et al., 2007). Another enzyme is SOD that catalyzes dismutation of the superoxide anion (O_2), which is detoxified to H_2O by catalase (Valavanidis et al., 2006). It is indicated that administration of GSPE accompanied with CDDP decrease the increment of hiobarbituric acid reactive substances (TBARS), increase the activity of catalase, SOD and GSH-dependent antioxidant enzymes (Saad et al., 2009); while activity of antioxidant enzymes is related to the levels of Cu and Zn (Badary et al., 2005).

Some phytoestrogens especially isoflavones found in soybean are useful in attenuation of the oxidative stress (Nitha et al., 2008; Zhu et al., 1999). The phenolic extract of soybean is protective against nephrotoxicity induced by CDDP and gentamicin (Ekor et al., 2006). Polyphenolic extract of soybean (PESB) inhibits renal xanthine oxidase activity (Ekor et al., 2010) and protects against kidney toxicity (Gulec et al., 2006). The extract of Rubia cordifolia has antioxidant effects and plays a protective role against loss of antioxidant enzymes such as GSH-dependent enzymes, catalase and SOD caused by CDDP administration (Joy et al., 2008). Large amounts of antioxidant components have been isolated from roots of Rubia and Curcuma comosa Roxb. These components include several types of anthraquinones such as 1-hydroxy-2-methylanthraquinone, nordamnacanthal, and diarylheptanoid that scavenge free radicals and decrease oxidative stress (Jariyawat et al., 2009; Tessier et al., 1981). In another study, low dose of pomegranate flower extract could ameliorate CDDP-induced nephrotoxicity via its antioxidant properties (Motamedi et al., 2014). It has been demonstrated that some plants containing phytoestrogens also have antioxidant effect because of their components such as isoflavonoids and trans-anethole (Mazaheri et al., 2013; Setchell, 1998). In addition, it has been demonstrated that phytoestrogens are beneficial for renal diseases (Velasquez et al., 2001). Trans-anethole as an agent with estrogenic activity could be found in high amounts in fennel essential oil (Devi et al., 1985; Farook et al., 1991). Although trans-anethole is also an antioxidant, it is seems that estrogen and trans-anethole do not affect the CDDP-induced nephrotoxicity (Devi et al., 1985).

It is clear that CDDP causes inflammation and genotoxicity (Jung et al., 2007; Pabla et al., 2008). Degradation of DNA is one of the most important reasons for cell death in renal tubules (Basnakian et al., 2005). It is demonstrated that CDDP polymorphonuclear leukocyte infiltration, which is indicated by increment of myeloperoxidase (MPO) activity (Pan et al., 2009). Previous researches have shown that Paeonia suffruticosa, grape seed, soybean, and Ginkgo biloba extracts have anti-inflammatory effect (Chacón et al., 2009; Ekor et al., 2010; Sohn et al., 2009; Song et al., 2013), and the extracts of grape seed, mushrooms, and carob could protect DNA from CDDP-induced injury (Elmhdwi, 2013; Gao et al., 2014; Nitha et al., 2008). CDDP can also increase inducible NO synthase (iNOS). In this regard, Song et al. reported that Ginkgo biloba can diminish NO production by inhibiting both gene expression and enzymatic activity of iNOS (Abd-Elhady et al., 2013; Song et al., 2013). Nigella sativa (Hadjzadeh et al., 2012), Garlic (Anusuya et al., 2013), Olive leaf (Kaeidi et al., 2016; Jafaipour et al., 2016) and Corcin (Naghizadel et al., 2008) also were studied by others to find their protective role against CDDP induced nephrotoxicity. Most herbal antioxidants that were subjected to use as supplement to protect the kidney against CDDP-induced toxicity have been demonstrated to have positive results. However, until now, there is no single acceptable herbal agent that is able to prevent CDDP nephrotoxicity to be recommended clinically.

NO on CDDP-induced nephrotoxicity

NO has been suggested to play an important role in CDDP-induced nephrotoxicity (Saad et al., 2001). NO is a key cellular factor synthesized by NO synthase from L-arginine (Nathan et al., 1994). NO possess both pro-apoptotic and anti-apoptotic functions; depending on the cell type and concentration of NO (Kolb, 2000). NO induces apoptosis by its ability to produce oxidative stress and activate caspase (Klein et al., 2003). In contrast, It has been reported that endogenous NO production or presence of appropriate amount of NO inhibits apoptosis both in in vivo and in vitro experimental models (Chung et al., 2001). It was previously reported that NO plays role in CDDP nephrotoxicity and usage of 2 - amino -4 - methylpyridin as a NOS inhibitor aggravates CDDP - induced nephrotoxicity (Saad et al., 2001).

Srivastava et al. showed that L-NG-nitroarginine methyl ester (L-NAME) as a nonselective NOS inhibitor attenuates CDDP-nephrotoxicity by reduction of BUN and Cr levels and lipid peroxidation (Srivastava et al., 1996). According to their report, CDDP increases the level of lipid peroxidation as well as NO and NOS activity, while L-NAME decreases amount of NO production in the kidney and liver. Thus, NOS inhibition may be helpful in prevention of developing toxic side effect of CDDP. This is while, it has been demonstrated that administration of L-arginine as the NO donor in rats treated with CDDP resulted in amelioration of indexes of CDDP-induced nephrotoxicity (Saleh et al., 2005). Also, intravenous injection of L-arginine accompanied by CDDP was demonstrated to lead to significant protection of kidney function (Quan et al., 1994). L-arginine also induces protective effects via increment of RBF, GFR, and vasodilator effect; so, L-arginine exerts its protective effects against CDDP-induced nephrotoxicity via hemodynamic and non-hemodynamic mechanisms (Quan et al., 1994). So far, the role of NO in experimental models remains controversial; non-protective role (Srivastava et al., 1996) or protective role (Mansour et al., 2002; Quan et al., 1994) against CDDP nephrotoxicity. It showed that mRNA and iNOS levels are increased in rats treated by CDDP and selective inhibitor of iNOS reduces CDDP-induced nephrotoxicity (Chirino et al., 2004; Chirino et al., 2008). They proposed that NO production is toxic and the main source of NO is iNOS (Chirino et al., 2008). NO produced under oxidative stress condition reacts with superoxide (O2-) and modifies biological molecules such as amino acids. It is demonstrated that there is enhancement of peroxynitrite (ONOO) production in CDDP-induced nephrotoxicity (Chirino et al., 2004).

It observed increment in mRNA levels of iNOS in the kidney 4 h after CDDP injection, and administration of iNOS inhibitor 3 days after CDDP injection prevented enhancement of Cr and BUN levels; decreased kidney tubules injury, and was protective against CDDP-induced oxidative stress and nitrosative (Deng et al., 2001). However, Saad indicated that inhibition of NOS aggravates kidney injury (Saad et al., 2001). This controversy may be related to the type of inhibitors. In addition, it is reported that the effect of L-arginine in CDDP-induced nephrotoxicity is gender-related (Eshraghi-Jazi et al., 2011) while L-arginine decreases the serum levels of BUN and Cr in male but not in female. Another study indicated that L-NAME promotes CDDP-induced nephrotoxicity in male rats (Moslemi et al., 2013).

Furthermore, it is demonstrated that aminoguanidine (AG) has protective effect against nephrotoxicity induced by CDDP (Mansour et al., 2002). AG is a compound structurally similar to L-arginine and inhibits iNOS (Misko et al., 1993). Administration of AG 5 days before and after single injection of CDDP reduces the rise in the serum levels of urea and Cr. AG also normalizes the decreased level of albumin (Misko et al., 1993). AG administration before and after CDDP normalizes urine volume, and pretreatment with AG decreases kidney mass and lipid peroxide. AG does not ameliorate the depletion of GSH content or the decrease in catalase activity induced by CDDP. They concluded that overproduction of iNOS might be the cause of several toxicities induced by CDDP. They proposed that the protective effect of AG may be related to its antioxidant effects and AG may be helpful as a protective agent against CDDP nephrotoxicity (Misko et al., 1993).

Gender difference in CDDP-induced toxicity

Gender difference in tumor growth process is one of the important subjects that is highlighted in clinical and experimental researches. A sex dimorphism in antitumor response to CDDP is observed in the growth of the Dalton's lymphoma where female mice show an accelerated tumor growth compared with male mice (Gupta et al., 2008). In CDDP therapy, the severity of weight loss, prolonged heat latency, sciatic motor nerve conduction velocity, and atrophy of nucleus and neuronal cell body were higher in males than females; while decrease in myelinated fiber diameter, myelin thickness, and myelinated fiber density were more significant in females (Wongtawatchai et al., 2009). Nephrotoxicity as a major side effect of CDDP found to be gender-related (Nematbakhsh et al., 2013a; Nematbakhsh et al., 2012c). CDDP increases the serum levels of BUN and Cr, kidney MDA levels, KTDS, kidney weight, and weight loss more in males than in females (Nematbakhsh et al., 2013a; Nematbakhsh et al., 2012c). In the study of Stakisaitis et al., male rats excreted more sodium after CDDP administration, and the Na/Cl ratio was significantly higher in male than female rats, which may be related to higher tubular toxicity in males (Stakisaitis et al., 2010). However, when CDDP is accompanied with different supplements, different results may observe in males and females. L-arginine shows protective effects against CDDP-induced nephrotoxicity in male rats; however, it promotes kidney injury in female rats (Eshraghi-Jazi et al., 2011). Losartan as an AT1R blockade has higher protective effects against CDDP-induced nephrotoxicity in males than females (Haghighi et al., 2012). Moreover, EPO in CDDP-treated animals fail to improve kidney damage in female rats, while it has protective effect against CDDP-induced nephrotoxicity in male rats (Eshraghi-Jazi et al., 2013). Furthermore, administration of vitamin E in CDDP-induced nephrotoxicity model decreases kidney injury and kidney dysfunction biomarkers to normal values in male rats but it does not have ameliorative effect on CDDP-induced toxicity in female rats (Jilanchi et al., 2013). Dexamethasone induces CDDP resistance in lung cancer cells in a gender dependent manner, and lung cancer cells in females show higher resistance to CDDP by dexamethasone as compared to those in males (Zhang et al., 2008b). It has been documented that serum nitrite concentration increases after CDDP administration in males but not in females, and co-administration of vitamin E and CDDP decreases the serum nitrite level in males while this was not the case in females (Nematbakhsh M, 2013a). Accordingly, CDDP-induced nephrotoxicity must be considered as a gender-related condition, and the exact underlying mechanisms should be determined. The most common organic cation transporter in kidney is organic transporter 2 (OCT2), which is expressed prominently in the basolateral membranes of proximal tubules. The action of OCT2 leads to accumulation of various cationic drugs as well as CDDP into proximal tubular epithelial cells, and stimulates CDDP-sensitive cells (Yonezawa et al., 2005). It is found that the expression level of renal OCT2 is higher in male rats (Urakami et al., 1999). It is indicated that up to 3 min after CDDP administration, the total clearance of CDDP is higher in male than female rats and the renal tissue uptake clearance of CDDP is greater in male than female rats (Yonezawa et al., 2005). Moreover, renal OCT2 expression decreases in castrated rats (Yonezawa et al., 2005), and it is reported that testosterone recovers renal OCT2 expression (Urakami et al., 2000). Administration of CDDP in tumor-bearing mice with Dalton's lymphoma indicated higher inhibition of tumor growth due to increased apoptosis and DNA fragmentation in male than female mice; while in vitro study indicated lower survival rate for male tumor cells in the proximity of CDDP (Gupta et al., 2008). In addition, the expression of p53 in the Dalton's lymphoma cell was higher in CDDP-treated male than that in female mice (Gupta et al., 2008). It is interesting that carboplatin toxicity can be affected by population and gender. It was shown that female Yoruban population (African descent) cell lines has lower sensitivity to carboplatin in comparison with male cell lines whereas in a European descent population gender difference was not seen (Huang et al., 2007), Also carboplatin IC50 (inhibition 50% cell growth) was higher in the African descent versus the European descent but this different was observed only in females of two strains (Huang et al., 2007). A study on the effect of CDDP-induced cytotoxicity on renal proximal tubular cells with different age, sex, and species (monkey and rat) indicated renal proximal tubular cells of the rats

have higher susceptibility to CDDP compared with those in monkeys; however, this study indicated sex and age are not associated with CDDP-induced renal proximal tubular cell injury in Sprague-Dawly rat (Lu et al., 2005). Furthermore, the different aspects of CDDP-induced toxicity in both genders may contribute to the phenotypic difference observed among the populations while gender difference has been shown in some populations and male gender is more susceptible to CDDP toxicity compared to female. Moreover, the probability of CDDP-induced nephrotoxicity is higher in male rats than females. This may be because of higher contribution of cationic transporter OCT2 in male gender than female or may be related to sex hormone alteration after CDDP injection.

CDDP therapy reduces testosterone levels (Imamura et al., 1996; Kinkead et al., 1992; Longo et al., 2011; Salem et al., 2012). Men in complete remission of testicular cancer for over two years show lowered testosterone levels (Wiechno et al., 2007). Also, 25-48% decrease in testosterone synthesis is reported in CDDP-therapy patients (Carreau et al., 1988). Decrease in testosterone level is accompanied with elevated levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in CDDP treatment (Aydiner et al., 1997; Malarvizhi et al., 1996a; Strumberg et al., 2002). Decreased activity of renal beta-glucuronidase during CDDP-treatment reflects the decreased availability of testosterone (Malarvizhi et al., 1996b). It is reported that CDDP suppresses the spermatogenesis and steroidogenesis by inhibiting the steroidogenic marker enzyme activity (Reddy et al., 2010). CDDP generates ROS that may inhibit testosterone production (Masubuchi et al., 2006; Mori Sequeiros GarcÃa et al., 2012). Testosterone supplementation was stated to reduce the side effects of CDDP (Vawda, 1994). Also, activity of renal beta-glucuronidase increases in rats supplemented with testosterone propionate (Malarvizhi et al., 1996b). The decreased microsomal enzyme activity is nearly restored when testosterone propionate is given once a day for 7 days after CDDP-treatment (Imamura et al., 1996). However, high dose of testosterone damages spermatogenesis in animals treated with low dose of CDDP (Aminsharifi et al., 2010). A recent study indicated that testosterone in low dose (physiologic dose) protects the kidneys against CDDP-induced nephrotoxicity; while high dose promotes nephrotoxicity (Rostami et al., 2014).

The effect of tamoxifen, as an estrogen antagonist receptor, on CDDP sensitivity has not indicated any correlation between tamoxifen effect on CDDP sensitivity and estrogen receptors, and this conception reveal that CDDP sensitivity of ovarian cancer cells are not linked with expression of estrogen receptors (Nowak-Markwitz et al., 2010). CDDP increases the level of FSH and decreases estradiol concentration in mice (LiNing, 2011). Also CDDP decreases ovarian and uterus weights, reduces the number of follicles and causes structural damage in the ovary; however, use of gonadotropin-releasing hormone (GnRH) combined with estrogen protects ovary against CDDP damage in mice (LiNing, 2011). CDDP and estrogen receptors bind with DNA, but CDDP decreases estrogen receptor affinity for DNA (Massaad-Massade et al., 2000). Effects of estrogen and CDDP on growth of human ovarian cancer cell line HO-8910 shows that 17-β estradiol does not inhibit the apoptosis but enhances proliferation of human ovarian cancer cell line HO-8910 (Grott et al., 2013). Vitamins E and C, and losartan have antioxidant and nephroprotective effects against CDDP, but this effect is abolished in the presence of pharmacological doses of estrogen (Nematbakhsh et al., 2012a). In addition, EPO has antioxidant, anti-apoptotic, and anti-inflammatory effects that result in nephroprotectant effect; however, it could not protect kidney against CDDP in the presence of estrogen (Pezeshki et al., 2012). Evaluation of estrogen role in CDDP-induced nephrotoxicity could not confirm the nephroprotective role of estrogen against CDDP although its cardioprotective effects is highlighted (Pezeshki et al., 2013). In addition, progesterone reduces the effect of CDDP in ovcar3 cells via progesterone receptor membrane component-1 (PGRMC1), because overexpression of PGRMC1 increases the cellular binding sites for progesterone and attenuates the killing effects of CDDP by about 50% while depleting PGRMC1 enhances the killing effect of CDDP in the presence of progesterone by 50%, and using PGRMC1 antibody in the presence of progesterone sensitizes the cells to CDDP (Peluso et al., 2008). It is also demonstrated that progesterone attenuates CDDP-induced toxicity in ovarian cancer cells via progesterone receptor (Zhu et al., 2013), and co-administration of high dose of progesterone (25 mg) (sustained-release pallet) and CDDP (2 mg/kg/week) increases platinum effect and facilitates CDDP toxicity in the two cell lines ovcar-3 and SKOV-3 in epithelial ovarian cancer cells and tumor genesis is suppressed by combination of CDDP and progesterone (Murdoch et al., 2008). Both estrogen and progesterone pretreatments result in resistance of A549 non-small cell lung cancer cells in vitro to CDDP and thus decrease CDDP-induced apoptosis, while this phenomenon is not antagonized by estrogen and progesterone antagonists such as ICI 182,780 and RU486 (Grott et al., 2013). Evaluation of oxytocin effect on CDDP-induced nephrotoxicity shows that oxytocin has a protective effect against CDDP-induced nephrotoxicity (Elberry et al., 2012).

It seems that interaction between CDDP and female sex hormones indicates that estrogen enhances CDDP sensitivity in tumor cells. At high pharmacological dose, it promotes kidney toxicity, but at low pharmacological dose has no effect on CDDP-induced kidney injury. Progesterone reduces the effect of CDDP in ovarian cancer cells and protects ovarian cancer cells from CDDP by progesterone receptor whereas co-administration of high dose progesterone and CP increases platinum effect and facilitates CDDP toxicity. Combination of estrogen and progesterone results in CDDP resistance and decreases apoptosis. Based on this result, the physiological or low pharmacological dose of progesterone and combination dose of estrogen and progesterone may protect kidney against CDDP. It also seems that keeping the sex hormone testosterone at the physiological level after CDDP therapy can help prevent CDDP side effects.

The results of many different researches in the laboratories and clinics were documented in the literature to show how the renal side effect of CDDP can be reduced.

Moreover, there are still many running researches to examine or to develop agents against CDDP-induced nephrotoxicity. Nevertheless, most experimental researches are designed in normal animals rather than in tumor models. The research on CDDP-induced nephrotoxicity cannot be stopped; however, It is the time to test the suggested supplements in real animal cancer models to make sure that the supplements do not reduce the direct effect of CDDP on tumors. In other words, an optimal candidate supplement should have two characteristics; protect the kidney against CDDP-induced toxicity, does not attenuate the direct effect of CDDP on the tumor (Wang et al., 2014).

Finally, according to this review several suggestions may provide to reduce CDDP induced nephrotoxicity:

1. CDDP induced nephrotoxicity is gender related. It seems female gender involves with the lower risk of nephrotoxicity after CDDP therapy.

2. Estrogen may increase the risk of renal toxicity after CDDP therapy, so CDDP therapy in women is recommended when the serum level of sex hormone estrogen in not high in the body.

3. To use the antioxidant as a supplementation to protect the kidney against CDDP induced nephrotoxicity, special care is needed. Some antioxidants have protective role to prevent CDDP induced nephrotoxicity in male, however the same antioxidants have not protective role against CDDP induced nephrotoxicity in female.

4. CDDP therapy has not only increased stress oxidative in the kidney as well as in the body, but also it disturbs renal hemodynamics, trace elements levels, RAS component, etc., Therefore and logically there is no expect to solve all the disturbances by one antioxidant supplementation. However, a suitable supplementation could reduce the progress of kidney toxicity after CDDP therapy.

5. According to previous studies, it is the time to select the few best protective agents which have the best laboratory evidences related to CDDP induced nephrotoxicity, and examine their protective role against CDDP induced nephrotoxicity in animals tumor models and design clinical trial studies to test the protective role of these agents in patients subjected to CDDP therapy.

Conflict of interest

The authors declare no conflict of interest.

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Review

Anti-Cancer and Protective Effects of Royal Jelly for Therapy-Induced Toxicities in Malignancies

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Abstract: Royal jelly (RJ) is a glandular secretion produced by worker honeybees and is a special food for the queen honeybee. It results in a significant prolongation of the lifespan of the queen honeybee compared with the worker honeybees through anti-inflammatory, anti-oxidant and anti-microbial activities. Consequently, RJ is used as cosmetic and dietary supplement throughout the world. In addition, in vitro studies and animal experiments have demonstrated that RJ inhibits cell proliferation and stimulates apoptosis in various types of malignant cells and affects the production of various chemokines, anti-oxidants and growth factors and the expression of cancer-related molecules in patients with malignancies, especially in patients treated with anti-cancer agents. Therefore, RJ is thought to exert anti-cancer effects on tumor growth and exhibit protective functions against drug-induced toxicities. RJ has also been demonstrated to be useful for suppression of adverse events, the maintenance of the quality of life during treatment and the improvement of prognosis in animal models and patients with malignancies. To understand the mechanisms of the beneficial effects of RJ, knowledge of the changes induced at the molecular level by RJ with respect to cell survival, inflammation, oxidative stress and other cancer-related factors is essential. In addition, the effects of combination therapies of RJ and other anti-cancer agents or natural compounds are important to determine the future direction of RJ-based treatment strategies. Therefore, in this review, we have covered the following five issues: (1) the anti-cancer effects of RJ and its main component, 10-hydroxy-2-decenoic acid; (2) the protective effects of RJ against anti-cancer agent-induced toxicities; (3) the molecular mechanisms of such beneficial effects of RJ; (4) the safety and toxicity of RJ; and (5) the future directions of RJ-based treatment strategies, with a discussion on the limitations of the study of the biological activities of RJ.

Keywords: royal jelly; 10-hydroxy-2-decenoic acid; anti-cancer effects; toxicities; malignancies

1. Introduction

The major therapeutic methods for patients with cancer are operations, chemotherapy and radiotherapy. In addition, molecular targeted therapy and immunotherapy are also commonly used for a variety of cancers. In patients with advanced or metastatic tumors, systematic therapies with anti-cancer agents are usually fundamental treatment strategies; however, the anti-cancer effects, including prolongation of survival, of such systematic therapies are not always satisfactory in clinical practice. In addition, chemotherapy and molecular targeted therapy results in relatively high frequency of adverse events, especially in elderly patients [1–3]. Therefore, many investigators, physicians and patients with cancer are particularly invested in the development of more effective and safer treatment strategies.

In general, natural products are advantageous because they are easily obtained and relatively safe. In addition, various natural compounds have been reported to be useful to improve the anti-cancer

effects of certain chemotherapeutic agents. In recent years, the consideration of natural products as anti-cancer treatments has grown worldwide [4–6]. Royal jelly (RJ) is of interest for the improvement of health and medicines. We have also dedicated specific attention to RJ in this review because of following reasons and findings: (1) RJ is special food for queen honeybee in both the larva and adult stages. As a result, it was speculated that RJ prolongs the lifespan of the queen honeybee relative to worker honeybees [7]. (2) RJ can modulate inflammation, oxidative stress and vasodilatory activity [8–12]. These RJ-induced activities are widely considered to be useful to maintain homeostasis and recover from pathological conditions; therefore, RJ has been used as cosmetics, health food, or dietary supplement [13,14], (3) RJ affects the immune system under various physiological and pathological conditions, including malignancies and stimulate not only immunocompetent cells but also antibody production [15–21]. Thus, RJ is speculated to modulate the wider immune system. (4) RJ has an abundance of the main nutrients, such as proteins, carbohydrates and lipids and has some stronger and specific biological activities compared to other bee products [17–19]. From these facts, there is a hypothesis that RJ may have some benefits for cancer treatments. However, we must note the decision of European Food Safety Authority (EFSA) that a cause and effect relationship cannot be established between the consumption of RJ and the claimed effects [20]. On the other hand, this opinion was published in 2011 and then new findings on beneficial effects of RJ for cancer treatments were showed by in vivo and in vitro studies.

In this review, we have first introduced the anti-cancer effects of RJ in in vivo and in vitro studies. Subsequently, we have summarized the usefulness of RJ in the prevention of anti-cancer treatment-induced toxicities in animal models and patients with cancer. In addition, we have shown the molecular mechanisms of the biological activities of RJ in cancer treatment. Finally, therapeutic strategies and the present use of RJ, its future direction and limitations of RJ-related activities have been discussed based on recent publications.

2. Anti-Cancer Effects of Royal Jelly and Its Components

RJ contains water, sugar, proteins and lipids and approximately 90% of RJ lipids are free fatty acids, containing 8–12 carbons that are usually either hydroxyl or dicarboxylic forms [21]. 10-hydroxy-2-decenoic acid (10-HDA), known as a major component of RJ, plays important roles in various biological activities, including inflammation and oxidative stress [22,23]. Therefore, in this section, we have discussed the reported anti-cancer effects of RJ and 10-HDA in various malignancies.

2.1. Anti-Cancer Effects of Royal Jelly

2.1.1. In Vitro Studies

First, the anti-cancer effects of RJ in cancer cell lines should be considered. Endogenous hormones are closely associated with carcinogenesis, tumor growth and progression in a variety of cancers, such as breast, ovarian and prostate cancer. It is well established estradiol plays crucial roles in the tumor development of breast cancer [24] and it is reported that RJ inhibits estradiol-induced cell proliferation of MCF-7 breast cancer cells [25]. In addition, these anti-cancer effects of RJ were mediated via the suppression of estradiol-related signaling in cell proliferation but not by binding of estradiol to the estrogen receptor [25]. This study also showed that such cancer cell proliferation was inhibited by RJ in the presence of bisphenol, which has environmental estrogen activity, even though RJ did not affect the proliferation in the absence of bisphenol. Essentially, it is speculated that RJ inhibits the proliferative activity of bisphenol in breast cancer cells. Finally, the authors commented that more detailed information on the active substance and physiological properties are important for the clarification of the anti-cancer effects of RJ and we support this opinion.

In contrast, there are no reports on the relationship between RJ and androgen-related tumor growth in prostate cancer. Similarly, the anti-cancer effect of RJ against hormone-dependent malignant behavior in cervical cancer is unclear, although bee bread, another bee product, was reported to inhibit

the tumor growth of HeLa cervical cancer cells [26]. However, the investigation of the effects of RJ in ovarian cancer has still not been performed. Unexpectedly, significantly inhibition of cancer-related characteristics is not commonly reported in the case of RJ monotherapy. For example, although several studies have shown that RJ tended to suppress the tumor growth of astrocytoma, glioblastoma multiforme, astroglia and colorectal cancer cells, these anti-cancer effects are not always recognized to be significant and RJ monotherapy is not recommended [27,28].

2.1.2. In Animal Experiments

In mouse model of breast cancer, orally administered RJ caused significant inhibition of tumor growth as a prophylactic-therapeutic method; however, such anti-cancer effect was not detected when administered following tumor cell inoculation [29]. Briefly, when mice injected subcutaneously with 4T1 mouse mammary tumor cells were treated with RJ for 14 days prior to the transplantation of tumor cells and subsequently for 28 consecutive days, the tumor volume was significantly lower than that in control mice; however, a corresponding inhibitory effect was not found when the mice were treated with RJ for 28 consecutive days after tumor cell transplantation. Thus, RJ intake may be effective as a prophylactic agent but not as a therapeutic agent; thus, the authors suggested that effective administration of RJ might require $\geq$14 days administration prior to tumor inoculation.

With regard to relationship between RJ administration and survival, it is reported that the administration of RJ can prolong survival compared to control animals and this effect occurred dose-dependently in a mouse model of Ehrlich ascites tumor [30]. In short, the highest protection conferred an extension of survival of approximately 38%, 71% and 85% for doses of 0.5, 1.0 and 1.5 g/kg for 33 days, respectively. Furthermore, this study suggested that a decrease in prostaglandin E (PGE)-2 might be associated with such anti-cancer effects in addition to immunity-related host resistance [30]. The PGE-2 system is recognized widely as stimulator of carcinogenesis, cancer cell proliferation and invasion and as an inhibitor of apoptosis in various types of cancers [31–33]. Furthermore, PGE2 is an important modulator for the activities of immune cells, including macrophages, dendritic cells and natural killer cells [34–36]. Thus, there is a possibility that RJ can improve the prognosis via the regulation of malignant aggressiveness and the immune system through the downregulation of PGE-2.

2.2. Anti-Cancer Effects of 10-Hydroxy-2-Decenoic Acid

10-HDA (Figure 1) is a major component of RJ and is known to have various biological activities [37].

Figure 1. Structure of 10-HAD.

The content of 10-HDA in RJ is reported to be 0.8%–6.5%; moreover, it is known as a unique component of RJ because it is not detected in any other natural raw material, even in other bee products [11,22,38]. To our surprise, anti-cancer effects of 10-HDA in leukemia and ascitic tumors were first reported in approximately 60 years ago [39,40]. In summary, these studies in mice showed that 1.5 mg of 10-HDA per milliliter of cell suspension completely prevented tumor formation in four types of malignant cells: mouse leukemia, 6CSHED lymphosarcoma, the TAS mammary carcinoma and the Ehrlich carcinoma [40]. Unfortunately, this did not prompt further immediate investigation into the anti-cancer effects or biological activities of 10-HDA. However, in recent years, there have been two in vitro studies point out that of the anti-proliferative activity of 10-HDA in colon cancer cells and it is known that the regulation of inflammatory functions or oxidative stress by 10-HDA is

an important mediator of these anti-cancer effects [12,28]. In contrast, although we already stated that RJ could inhibit the bisphenol-induced proliferation of breast cancer cells, 10-HDA does not exhibit similar anti-proliferative activity [25]. Thus, the information on the anti-cancer effects of 10-HDA is incomplete and more a detailed analysis at molecular levels in more types of malignancies is necessary to confirm the utility and limitations of 10-HDA as a therapeutic agent.

3. Activity of Royal Jelly against Cancer Therapy-Induced Toxicity

Chemotherapy usually leads to various adverse events, such as bone marrow suppression, gastrointestinal tract disorders, dysfunction of the kidney and the liver, owing to the lack of tumor specificity and the resultant effects on normal tissues. The adverse events caused by systematic cancer therapy are unavoidable, although the symptoms and degrees are dependent on the individual. Decreasing the incidence and severity of adverse events induced by anti-cancer therapies is of great importance for the maintenance of the quality of life (QOL) of patients with cancer. It is also important for the improvement of anti-cancer effects and the prolongation of survival: essentially, some patients are prevented from continuing effect treatment owing to the severe adverse events experienced. It is reported that some anti-cancer agents cause significant adverse events, even when administered at a low dosage [41,42]. Therefore, development of agents that decrease such toxicities is important and currently a major topic of cancer research. In addition, many investigators have given special attention to pharmacotherapy using natural substance as promising future therapeutic options. In this section, the suppressive roles of RJ against cancer therapy-induced toxicities obtained from in vivo studies.

3.1. In Animal Models

Pulmonary fibrosis, one of the most severe adverse events in patients treated with bleomycin (BLM), is associated not only with a reduced QOL but with lethal respiratory discomfort. In rats, cell count and content of pro-inflammatory and pro-fibrotic cytokines in the bronchoalveolar lavage fluid (BALF) were increased by the administration of an intra-tracheal instillation of BLM (7.5 IU/kg); however, such pathological increases were reversed by the oral administration of RJ (50 and 100 mg/kg) for 7 days consecutively prior to BLM administration [43]. In addition to such biochemical markers, they also reported that RJ suppressed histological alterations induced by BLM [43]. Unfortunately, there is little information on the anti-fibrotic effects of RJ or other components in bee honey in BLM-induced pulmonary fibrosis. RJ was also reported to improve serum testosterone level and sperm parameters in rats treated with BLM [44]. The authors speculated that the anti-oxidant properties of RJ exerted positive effects on these parameters [44].

Cisplatin (*cis*-diamminedichloroplatinum; CDDP) is an effective synthetic-spectrum anti-cancer agent and is often included in standard regimens for many solid tumors. However, the clinical usefulness and anti-cancer effects are often restricted owing to the wide variety of adverse effects observed, such as nausea, neurotoxicity, alopecia and fatigue. Nephrotoxicity and hepatotoxicity are the most important of these events [45,46], because they can be fatal to patients with cancer. Consequently, the suppression of these major events caused by CDDP may improve the anti-cancer effect of the drug. With regard to nephrotoxicity, several studies have reported that RJ conferred protective effects on renal function during CDDP treatments in experimental animals [47–49]. In short, serum creatinine levels in rats administered a single oral dose of RJ (300 mg/kg) for 15 days consecutively following a single intra-peritoneal injection of CDDP (7 mg/kg) (2.15 $\pm$ 0.55 mg/dL) were significantly ($p < 0.05$) lower than those administered CDDP alone (3.15 $\pm$ 0.50 mg/dl) [47]. Others report also showed similar results, with pre-treatment (1 h prior to intra-peritoneal administration of 1 mg/kg CDDP kg) with 100 mg/kg RJ reversed the changes in serum parameters, including urea, creatinine and uric acid, observed after CDDP treatment alone [49]. These studies also showed that CDDP led to significant histological changes of congestion, dilatation, epithelial vacuolization and infiltration of some immune cells, mostly macrophages, lymphocytes and plasma cells in the kidney tissues; however, these changes were decreased by RJ [47,49]. In a discussion of the hepatotoxicity, Karadeniz et al. [47]

reported that the serum ALT concentration in rats administered CDDP and RJ (29.50 ± 1.70 IU/L) was significantly lower than in rats administered CDDP alone (80.50 ± 2.50 IU/L). The authors commented that such protective functions for the kidney and liver may be due to the anti-apoptotic, anti-oxidant and free radical-scavenging activity of RJ and its compounds [47,48]. Furthermore, RJ suppressed CDDP-induced testicular damage in a rat model [50]. In this study, RJ administration led to a decrease in the malondialdehyde level and an increase in superoxide dismutase, catalase and glutathione-peroxidase activities; in addition, the authors commented that RJ may suppress CDDP-induced sperm toxicity owing to its antioxidant activities.

Cyclophosphamide is a cytotoxic alkylating agent that it is often used for the treatment of cancer. In a rat model, RJ showed significant protective effects against cyclophosphamide-induced prostate cancer damage [51] and oral RJ administration to rats protected against the histological damage to the small intestine induced by methotrexate (MTX), which has anti-cancer effects via folate antagonist activity [52]. In short, mucosal thickness, villus length, villus length/crypt ratio and semi-quantitative histological evaluation in rats treated with MTX was significantly difference to those treated with MTX and RJ [52]. In addition, such protective effects observed in the small intestine after 100 mg/kg RJ administration were higher than those after 50 mg/kg administration [52]. These two different studies showed that part of the protective effects in the prostate and small intestine was potentially associated with the regulation of oxidative stress [51,52].

The compound paclitaxel is extracted from the Pacific yew tree *Taxus brevifolia* and exerts anti-cancer activity via tubulin binding to inhibit the disassembly of microtubules. It is commonly used for conventional therapies and has been the subject of clinical trials for the treatment of various types of malignancies [53]. It is reported that RJ administration protected against paclitaxel-induced histopathological injury, such as diffuse edema, hemorrhage, congestion, hyaline exudates and necrosis and cardiac biomarkers of the creatine kinase level via the suppression of oxidative and nitrosative stress [54].

Unfortunately, there are few reports on the protective effects of RJ against toxicities induced by molecular targeted therapy or immune checkpoint inhibitors in animal models. We believe that more detailed studies about such issues are important.

3.2. In Patients with Malignancies

Oral mucositis and gastritis are common adverse events in patients with cancer treated with anti-cancer therapies, including chemotherapy, radiotherapy and molecular targeted therapy [55,56]. It is recognized as one of the most noteworthy adverse events because it may result in a decrease in QOL or the rate of completion of therapy. Various clinical trials on the prevention of mucositis induced by anti-cancer therapies are ongoing [56–58]. For example, in patients with head and neck cancer, a randomized single (physician)-blind trial with an RJ-treated group (n = 7) and a control group (n = 6) was performed to evaluate the clinical utility of RJ for the prevention of oral and esophageal mucositis [59]. In this study, all patients were treated with radiotherapy (66–77 Gy) and chemotherapy (nedaplatin and docetaxel, S-1, or intra-arterial CDDP); in addition, patients in the RJ group took RJ (3 g/day) during radiation therapy. Their results showed that all patients in the control group experienced grade 3 mucositis, which progressed to grade 4 in one patient at 1 month after treatment but that grade 3 mucositis was observed in only 71.4% of patients in the RJ group. In this study, we should note that further studies are needed because of the small sample size and the absence of double blinding. Finally, the authors concluded that prophylactic use of RJ was effective for the reduction of mucositis induced by chemoradiotherapy in these patients.

With regard to the protective effect of CDDP-induced nephrotoxicity, a comparison of the treatments of crude honey, RJ and control was performed in 30 patients with cancer treated with CDDP; randomly divided into the honey group (n = 10) and the RJ group (n = 10), which were pre-treated before the initiation of CDDP and during CDDP treatment and the control group (n = 10) administered CDDP only [60]. This study showed a significant decreased ($p < 0.05$) of serum levels

of creatinine and urea before and after treatment in the honey group. However, a similar significant improvement of kidney function parameters was not found in RJ group. In addition, it was shown that a remarkable reduction in these kidney function parameters occurred in 60% of patients in the honey group but only in 40% of patients in the RJ group. The authors speculated that the small sample size may be the explanation for this difference and suggested that further investigation with a larger sample size should be conducted to confirm this issue. In addition, we suggest that a more detailed analysis, including dosage, duration and timing of administration also should be performed. Furthermore, we also speculated that there was the possibility that crude honey, including various honey products such as propolis and bee pollen, is more closely associated with nephroprotective effects more than pure RJ because these products exert protective effects on kidney function [61,62]. Indeed, as mentioned above, animal experiments also showed that the nephroprotective effects of RJ were lower than those of honey [49].

A double-blind randomized clinical trial was performed to evaluate the effectiveness RJ on the symptoms of cancer-related fatigue in patients administered anti-cancer therapies [63]. In this trial, 52 patients were invited into two groups: the study group was treated with processed honey and RJ (n = 26) and the control group was treated with pure honey (n = 26); supplements of 5 mL were administered twice per day for 4 weeks. All three scores of fatigue and performance status in the study group were significantly better than those in control group [63]; however, the authors indicated that further clinical trials with a larger number of patients and a longer duration of intervention are necessary to clarify the role of RJ in managing cancer-related fatigue, because their study populations included a variety of malignancies and treatments. In addition, we should note that honey and RJ but not only RJ, was used in this clinical trial.

Finally, we have summarized previous reports on the suppression of toxicities by RJ in malignancies in Table 1.

Table 1. Effects of royal jelly on anti-cancer agent-induced toxicities.

Toxicities	Agents	Objective	Summary of Effects	Reference
Pulmonary Fibrosis	Bleomycin	Rat	Attenuated oxidative damage and fibrosis	[43]
Oral Mucositis	5-Fluorouracil	Hamsters	Ointments significantly and dose-dependently improved the recovery from damage	[64]
	Radiation and chemotherapy	One hundred and three patients	Improved the signs of oral mucositis and shortened its healing time	[65]
	Chemoradiation therapy	Thirteen head and neck cancer patients	Reduced the toxicity in by RJ in randomized clinical trials.	[59]
Intestinal Damage	Methotrexate	Rats	Suppressed damage through an increase in the activities of anti-oxidant factors	[52]
Cardio-Toxicity	Paclitaxel	Rats	Conferred protection against histopathological and biochemical alterations	[54]
Nephro-Toxicity	Cisplatin	Rats	Inhibited elevation of serum creatinine and prevented histological alterations.	[47]
	Cisplatin	Rats	Histopathologic findings and oxidative parameters were partially reversed	[48]
	Cisplatin	Rats	Reversed the changes in serum creatinine, urea and uric acid.	[49]
	Cisplatin	Thirty-two patients	Serum creatinine and urea were not changed before and after the treatment.	[60]
Hepato-Toxicity	Cisplatin	Rats	Inhibited elevations of serum markers and histological alterations.	[47]
Fatigue	Hormone therapy, chemotherapy and radiotherapy	Fifty-two patients	Ameliorated toxicity in a double-blind randomized study	[63]
Testis Damage/Fertility	Cisplatin	Rats	Histopathologic findings in the testes were partially reversed	[48]
	Bleomycin	Rats	Improved serum levels of testosterone and sperm parameters	[44]
Prostate Damage	Cyclophosphamide	Rats	Protected against drug-induced prostate tissue damage.	[51]

3.3. Molecular-Level Changes Induce by Royal Jelly

In this section, we have introduced the molecular mechanism for the prevention of such cancer therapy-induced toxicities (Table 2).

Table 2. Molecular-level changes induced by royal jelly in response to anti-cancer therapies.

Molecules	Organs	Species	Agents	Change	Reference
Apoptosis					
Bax	Prostate	Rats	Cyclophosphamide	↓	[51]
Bcl-xL	Kidney, liver	Rats	Cisplatin	↑	[47]
Caspase-3	Kidney, liver	Rats	Cisplatin	↓	[47]
Proliferation					
BrdU	Kidney	Rats	Cisplatin	↑	[49]
Inflammation					
CRP	Serum	Rats	Cyclophosphamide	↓	[51]
TNF-α	Serum	Rats	Cyclophosphamide	↓	[51]
	BALF	Rats	Bleomycin	↓	[43]
Oxidative stress					
eNOS	Prostate	Rats	Cyclophosphamide	↓	[51]
GSH	Kidney	Mice	Cisplatin	↑	[66]
	Kidney, liver	Rats	Cisplatin	↑	[47]
GSH-Px	Prostate	Rats	Cyclophosphamide	↑	[51]
	Kidney, liver	Rats	Cisplatin	↑	[47]
	Lung	Rats	Bleomycin	↑	[43]
	Plasma	Rats	Methotrexate	↑	[52]
GST	Kidney, liver	Rats	Cisplatin	↑	[47]
MDA	Kidney	Mice	Cisplatin	↓	[66]
	Kidney, liver	Rats	Cisplatin	↓	[47]
	Lung	Rats	Bleomycin	↓	[43]
	Plasma	Rats	Methotrexate	↓	[52]
SOD	Kidney, liver	Rats	Cisplatin	↑	[47]
	Plasma	Rats	Methotrexate	↑	[52]
Fibrosis					
α-SMA	Kidney	Rats	Cisplatin	↓	[49]
IFN-γ	BAL	Rats	Bleomycin	↑	[43]
TGF-β1	Kidney	Rats	Cisplatin	↓	[49]
	BALF	Rats	Bleomycin	↓	[43]

Bax, Bcl2-associated X protein; Bcl-xL, B-cell lymphoma-extra-large; BrdU, Bromodeoxyuridine; CRP, C-reactive protein; TNF, tumor necrosis factor; BALF, bronchoalveolar lavage; eNOS, nitric oxide synthase; GSH, glutathione; GSH-Px, glutathione peroxidase; GST, glutathione-S-transferase; MDA, malondialdehyde; SOD, superoxide dismutase; SMA, smooth muscle actin; IFN, interferon; TGF, transforming growth factor. ↓, Decreased molecular change by chemotherapeutic agents; ↑, Increased molecular change by chemotherapeutic agents.

3.3.1. Apoptosis and Proliferation

Many types of chemotherapeutic agents induce apoptosis, not only in malignant cells but also in normal cells. In fact, CDDP remarkably increased the expression of caspase-3, which is a key

mediator of apoptosis, in the kidney and liver of rats. However, RJ treatment decreased such caspase-3 reactivity in the proximal tubules of tissues of the kidney and the liver [47]. In contrast, the same study showed that the reactivity of Bcl-xL, which is an inhibitor of apoptosis, was lower in the kidney and liver of rats treated with CDDP than in control rats and that this decrease in reactivity was restored in rats treated with CDDP and RJ [47]. Other investigators have reported that cyclophosphamide increased the expression of Bax, which is a stimulator of apoptosis, in most of the prostatic acini of rats; however, the cyclophosphamide-induced change in Bax expression was improved by the concomitant administration of CDDP and RJ [51]. In addition, this study showed that although CP led to marked morphological changes, such as cystic dilatation with lost papillary fold in acini, flattened lining epithelium, wall integrity and apparent rupture of some acini, these changes of pathological features were suppressed by RJ via the modulation of Bax immunoreactivity [51].

With regard to cell proliferation, there was a report that the expression of bromodeoxyuridine (BrdU), which is commonly used as a marker of cell proliferation, was downregulated in renal tubular epithelial cells by CDDP administration in rats; however, this change was restored by dietary RJ administration [49]. Thus, in animal models, RJ protects from pro-apoptotic activity and the anti-proliferative effects caused by a variety of anti-cancer agents in several normal tissues.

3.3.2. Inflammation and Oxidative Stress

Inflammation and oxidative stress are closely associated with anti-cancer agent-induced toxicities [67,68]. RJ has important roles in the regulation of inflammation and oxidative stress under various physiological and pathological conditions and the beneficial changes in the relevant molecules are thought to be modulated by RJ [8–12].

Oxidative stress is associated with pathological conditions, including disorders of various organs and tissues [69,70]; conversely, anti-oxidants are speculated to prevent oxidative stress-induced damage [71,72]. Glutathione (GSH), glutathione peroxidase (GSH-Px), superoxide dismutase (SOD) and glutathione-S-transferase (GST) are known endogenous anti-oxidants and anti-oxidant parameters [72]; increased levels and activities of these factors were detected in the kidney and the liver of rats treated with CDDP and RJ compared with those administered CDDP alone [47]. In addition, this study also showed that levels of malondialdehyde (MDA), which is commonly used as biomarker of oxidative stress [73], were significantly lower in the kidney or liver tissues of rats treated with CDDP and RJ than those treated with CDDP. Other investigators also showed similar significant changes in GSH and MDA levels in the kidney tissues of mice [66]. Furthermore, it was also reported that RJ decreased the tissue content of MDA, which was increased by an anti-cancer agent, in the lung tissue of rats treated with bleomycin [43]. The GSH-Px level in the prostate was significantly higher in rats administered with cyclophosphamide and RJ than those administered cyclophosphamide only [51] and similar findings was also reported in the lung of rats treated with bleomycin [43]. In rats treated by MTX, the plasma MDA levels in the MTX and RJ-treated group were significantly lower than those in the MTX-treated group and the plasma levels of SOD and GSH-Px in the MTX and RJ-treated group were higher than those in MTX-treated group [52]. Thus, their results support the role of RJ as an anti-oxidant in response to the oxidative stress caused by a variety of anti-cancer agents.

In the endothelial cells of rat prostate tissues, eNOS expression in the cyclophosphamide and RJ-treated group was significantly lower than that in cyclophosphamide group [51]. Unfortunately, the relationship between such changes and anti-cancer agent-induced toxicities in normal tissues is not well characterized. However, it is possibility that this mechanism may affect the pathological mechanisms of some toxicities owing to the important role of eNOS in endothelial cell survival and angiogenesis [74].

With regard to inflammation, it has been reported that cyclophosphamide (CP) increased the serum levels of c-reactive protein (CRP) and tumor necrosis factor (TNF)-α in rats; however, such an increase was not observed in rats orally administered RJ (300 mg) for 14 days by gastric tube, followed by administration of CP [51]. However, a similar result was reported in TNF-α levels in

the bronchoalveolar lavage fluid (BALF) of rats treated with bleomycin [43]. Briefly, rats were orally administered RJ orally (50 and 100 mg/kg/day) for 7 days consecutively before the administration of single intratracheal instillation of bleomycin at 7.5 IU/kg and RJ reversed the change in TNF-α levels in BALF. Interestingly, it was also shown that RJ reversed the histopathological alterations induced by BLM and increased the anti-fibrotic cytokine, interferon (IFN)-γ, in BALF that was decreased by BLM [43].

3.3.3. Fibrosis

Fibrosis is closely associated with not only dysfunction of many organs but also tumor progression in various types of cancers [75,76]. Therefore, the appropriate regulation of fibrotic changes by cancer-related factors and anti-cancer therapies is important for the maintenance of homeostasis and to improve the prognosis in patients with cancer. Indeed, many investigators have specifically investigated the molecular mechanisms and preventive strategies of fibrosis in various organs [77,78].

However, there are only a few reports of the changes in fibrosis-related factors caused by RJ administration in vivo. One report showed that that intra-peritoneal CDDP administration (1 mg/kg twice weekly for 10 weeks) damaged 60% of renal tubules in rats (Ibrahim) and fibrogenic factors, including α-smooth muscle actin (SMA) in the interstitial tissues and transforming growth factor (TGF)-β1 in renal tubules, were upregulated by this treatment. However, dietary RJ decreased CDDP-induced α-smooth muscle actin and TGF-β1. The induction of such changes at the molecular level by RJ are speculated to confer the protective effects of renal function because such pro-fibrotic changes are closely associated with CDDP-induced nephrotoxicity [77]. Other investigators have also shown that RJ reversed TGF-β levels in the BALF of rats treated with BLM [43]; unexpectedly, they also found that significant activity was detected in in rats orally administered RJ at 50 and 100 mg/kg/day but not at 25 mg/kg/day.

4. Therapeutic Strategies for Royal Jelly in the Near Future

Natural products, including RJ, have been investigated for their promise as potential agents for the therapy of patients with malignancies. Indeed, as mentioned above, inhibitory effects, such as the prevention of tumor growth and invasion, have been confirmed by in vivo and in vitro studies. However, many investigators and clinicians feel that the anti-cancer effects exerted by crude RJ alone are far from satisfactory for the required improvements in prognosis and survival. Therefore, various challenges and clinical trials have been performed, as follows.

Previously, we introduced combined therapies of RJ and other anti-cancer agents. For example, it is reported that the cytotoxic effect of temozolomide (TMZ), which is an alkylating cytostatic drug, in a human glioma cell line was increased by the combination of TMZ and RJ [27]. Briefly, the combination of TMZ with honey, beebread and RJ, exerted stronger cytotoxic activity on human glioblastoma multiforme cells (U87MG) than TMZ alone. In contrast, their results also showed that similar cytotoxic efficacy of the combination therapies was not detected in diffuse astrocytoma cells [27]. Other investigators showed that the combined therapy of RJ and IFN-α demonstrated anti-proliferative activity for the colorectal cancer cell line (CaCo-2) [28]. Interestingly, their study also showed that the highest anti-proliferative activity was obtained when RJ and IFN-α were applied at the ratio 2:1, in a comparison of the ratios of 1:1 or 1:2 [28].

Furthermore, there have been several reports on the anti-cancer and biological effects of mixtures of natural products that contain RJ. For example, GE132+Natural, which is a novel supplement consisting of five compounds (resveratrol, *Ganoderma lucidum*, sulforaphane, lycopene and RJ) showed anti-proliferative effects against cell lines of breast cancer (MCF7), colon cancer (SW480) and prostate cancer (PC-3) in a dose-dependent manner, although it did not affect the proliferation of mesenchymal stem cells and the peripheral blood cell count [79]. Furthermore, there was a report that 100 mg/kg RJ and green tea extracts protected CDDP-induced nephrotoxicity via the restoration of GSH content and MDA production in mice [66]. Thus, a combination of natural products may have suitable anti-cancer

effects and protective effects against drug-induced toxicities. However, there is unfortunately little information available from in vivo and in vitro studies or clinical trials.

Several reports have also suggested that some fractions of RJ are potential therapeutic agents for various types of malignancies. For example, there is a report that among the two protein fractions obtained from the protein extract of RJ precipitated with 30% and 60% ammonium sulfate (called RJP_{30} and RJP_{60}, respectively), the survival of human cervical cancer cells (HeLa) was inhibited by RJP_{30} but not by RJP_{60} [80]. More recently, the lipophilic fraction of RJ was reported to have extraordinary anti-proliferative activities in a neuroblastoma cell line (SH-SY5Y) compared with hydrophilic fraction [81]. In addition, this study also found that the biological activities in neuroblastoma cells were stronger than those in immortalized murine myoblasts and prostate cancer cells. Thus, we also agree with their opinion that the search for more effective and disease-specific fractions of RJ may be critical for improvements in the anti-cancer effects.

At present, various chemical substances and environmental hormones that are present in a variety of plastic products, food and beverage containers and many products in house and work place, are speculated to be associated with tumorigenesis [25,82]. Substances with detoxification activities against such chemicals and hormones have not yet been identified; however, mitigation strategies using natural products are currently under investigation [82]. With regarding RJ, it is reported that RJ has anti-environmental estrogen activity against effects induced by bisphenol A (BPA) in MCF-7 human breast cancer cells. In brief, the number of MCF-7 cells was significantly increased by exposure to 1000 nM BPA for 72 h; however, this increase was inhibited by processed RJ (0.1 g dissolved in 10 mL PBS, centrifuged at 15 kg for 15 min and the top clear layer was used) [82].

5. Safety of Royal Jelly

RJ is recognized widely as a safe agent in previous studies. Briefly, in a mouse model, the oral administration of 10 g/kg RJ showed no acute toxicity [83]. In addition to acute reactions, RJ administration by gavage did not cause significant changes of serum creatinine, AST and ALT in rats, or alter the histological structure of the kidney and liver [47]. In addition, the same study confirmed that number of apoptotic cells and immunoreactivities of apoptosis-related molecules, such as caspase-3 and Bcl-xL, in the kidney and liver tissues was not changed by RJ. Furthermore, the oral intake of RJ 1.0 g/kg/day for 33 days consecutively did not affect PGE2 production in the supernatant from the peritoneal washes of normal mice [30]. In regard to oxidative stress, RJ was shown to exert no significant influence on MDA and GSH levels in the kidney of mice under physiological conditions [66]. Thus, there is a consensus that RJ is safe as a supplement and drug for clinical use under proper conditions.

However, we would recommend attention is paid to the following reports. At first, although oral RJ intake did not affect the weight of the lung and the kidney, the weights of the thymus and the spleen were reduced [29]. In this report, the authors commented that changes in the function of the spleen and the thymus by cell-mediated and humoral immunity might be associated with such phenomena and the precise effects of RJ on the immune system required further study [29]. Next, other investigators showed that approximately 10% of the renal tubules had CDDP-induced histopathologic change-like alterations, including moderate changes in rats treated with RJ, although serum parameters of renal function were not significantly altered [49]. Finally, there is the opinion that RJ contains growth factors or hormones that promote the cell growth of adipocytes [80]. These reports do not indicate that RJ has significant toxicities or propensity to cause adverse events; however, more detailed and broader information on the biological effects of RJ at molecular, pathological and clinical levels should be collected for normal cells, tissues and organs.

6. Limitations of Studies on Biological Activities of Royal Jelly

The contents of honey are variable and depend on the honeybee subspecies, regional plans and flower pollen [84,85]. Similarly, the biological roles and composition of various fractions of RJ are

affected by such factors. Indeed, RJ composition varies by countries; for examples, the percentage of 10-HDA content in Brazil tended to be higher than that in other countries, including Japan, India, Turkey and Switzerland [38]. Furthermore, although it was reported that RJ (0.5–1 mg/mL) enhanced MCF-7 cell proliferation owing to the estrogenic activities of RJ via interaction with estrogen receptor [86], other investigators did not find similar pro-carcinogenic and estrogen-like activities by RJ supplied by other manufacturers [25]. With regard to honey, manuka honey is produced in New Zealand by bees that pollinate the native manuka bush and was shown to prevent CDDP-induced histopathological changes in the liver and suppressed the changes seen in the kidneys; however, Talh honey, one of the most commonly consumed honeys in Saudi Arabia, decreased CDDP-induced liver histopathological changes but had no effect on CDDR-induced kidney changes in model rats [87]. Therefore, it is difficult to compare the protective effects from harmful phenomena and the anti-cancer effects of RJ between different studies. We support the opinion that the influence of these factors should be noted in the discussion and comparison of biological activities of honey products [19].

It was also reported that the administration route of RJ affects its anti-cancer effects. For example, in murine mammary carcinoma models, the intraperitoneal or subcutaneous administration of RJ did not affect metastasis formation, whereas intravenous administration prior to tumor cell inoculation significantly inhibited the formation of metastases [88]. In general, RJ is administered orally when used as a supplement and a prophylactic because of simplicity. However, when the clinical trials of RJ-based therapy are planned, the administration method may be an important determinant of its success. In contrast, there is no general agreement on the best administration method to produce the anti-cancer and/or protective effects of RJ in patients with malignancies. Thus, many issues remain to determine the clinical usefulness of RJ in these patients.

7. Conclusions

In this review, we have summarized studies on the anti-cancer effects of RJ reported in in vivo and in vitro studies. RJ and its main component, 10-HDA, can inhibit tumor growth and cancer cell invasion via the regulation of various cancer-related factors. In addition, animal experiments have shown that RJ administration leads to prolonged survival with a variety of malignancies. Many reports demonstrated that RJ is useful for protection against anti-cancer agent-induced toxicities, such as mucositis, fibrosis and disorder of the kidney and the liver. Furthermore, the modulation of various biological activities by RJ, including cell survival, inflammation and oxidative stress, is closely associated with the RJ-induced effects. Several clinical studies have confirmed the efficacy of RJ against drug-induced toxicities and clarified the mechanisms in patients with cancer; however, almost all of these clinical trials used relatively small study populations. Therefore, more detailed investigations are essential for a discussion of the clinical utility of RJ in these patients. The efficacy and safety of various combination therapies based on RJ and anti-cancer drugs, using various fractions of RJ, have been reported in vivo and in vitro. Although it is certain many problems remain to be solved, we believe that RJ is a potential tool for the improvement in the QOL and prognosis of patients treated with anti-cancer therapies.

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