

Review Article



A Glance on Medical Applications of *Orthosiphon stamineus* and Some of its Oxidative Compounds

Manaf Almatar*, Harith Ekal, Zaidah Rahmat

Faculty of Biosciences and Medical Engineering, Department of Biotechnology and Medical Engineering, Universiti Teknologi Malaysia (UTM), Johor Bahru, Johor, Malaysia.

*Corresponding author's E-mail: manafmatar@yahoo.com

Accepted on: 14-11-2013; **Finalized on:** 31-01-2014.

ABSTRACT

Used in several countries to Southeast Asia (particularly in Malaysia, Indonesia, Thailand and Myanmar) as traditional medicine, *Orthosiphon stamineus*, which belongs to Lamiaceae family, has been extensively studied due to its wide range of medicinal properties. Generally, *Orthosiphon stamineus* is consumed as a herbal tea. It is believed that *Orthosiphon stamineus* leaves have diuretic properties and has been used to remove stones from the kidneys. It is also widely applied to cure rheumatism, fever, hepatitis, gallstones, eruptive, hypertension, diabetes, epilepsy and eruptive as well as promoting health and well-being. Moreover, *Orthosiphon stamineus* is rich in the active chemical compounds such as stereos, oleanolic acid, polyphenols, flavonoids and terpenoids. Polyphenol, which is the most dominant compound in *Orthosiphon stamineus* leaves, prevents the formation of lipid peroxidation products in the biological system, and has a considerable role in reducing oxidative stress. Furthermore, high amount of flavonoids such as eupatorin (EUP), sinensetin (SEN), rosmarinic acid (RA) and quercetin (Q) was also detected in different tissues of this plant. In this review we attempt to summarize the medical properties of *Orthosiphon stamineus* with its oxidative compounds.

Keywords: *Orthosiphon stamineus*, Antioxidant, Rosmarinic acid, Quercetin.

INTRODUCTION

Many years ago, herbs are considered as the main source for drugs and nowadays herbal medicine becomes more popular as an alternative form of health care in all over the world^{1, 2}. Particularly, *Orthosiphon stamineus* which is commonly known as "MisaiKucing" is one of the oldest popular medicinal plants that grown in southeast Asia such as Malaysia, Indonesia, Thailand, Vietnam, and neighboring countries³. Lamiaceae family contains many species of medicinal plants, one of them is *Orthosiphon stamineus* which has special chemical and pharmacological properties^{4, 5}. The leaves of "MisaiKucing" (Malay for "Cat's Whiskers") is commonly used as Java Tea that appears in many products where safe diuretic action is required like in hypertension, kidney stones, water retention, diabetes, detoxification and rheumatism. The products have many different forms such as tablets, tea sachets, raw herbs capsules, and dried leaves or extracts^{6, 7}. In addition, antioxidant properties of this plant play a critical role of their therapeutic activity⁸.

A wide range of flavonoids were detected in various tissues of *Orthosiphon stamineus* such as rosmarinic acid (RA), quercetin (Q), eupatorin (EUP) and sinensetin (SEN)⁹. Phenolic compounds acquire many biological events such as anti-carcinogenic, anti-inflammatory, and anti-atherosclerotic activities¹⁰. In this review, the summary of the medical properties for this plant and its oxidative compounds will be elucidated.

APPLICATIONS OF *ORTHO SIPHON STAMINEUS*

In southeast Asia *Orthosiphon stamineus* is one of the species that extensively used as a traditional medicine for numerous disorders and diseases such as high blood pressure, arthritis, kidney stones, rheumatism, diabetes and probably aiding in the cure of other types of illness as well¹¹. Furthermore, consuming the herbal extract can improve the body's metabolism which turn into more expended calories and triggers the body to sweat more¹². However, the use of "MisaiKucing" extracts can reduce or extents help to cure some of the ailments aforementioned and are described as follows:

Kidney Stones

Kidney stones are defined as the production of crystals of minerals which are stored and retained in the kidneys¹³. Thus, individuals who suffer from this event will feel pain and discomfort, particularly the surrounding area of the kidneys. One of the important factors involved in the forming of the renal stones is the lack of water consumption. When water is consumed less, the urine concentration will tend to rise over than the normal levels and this situation will increase the possibility of the formation of kidney stones and its development. Additionally, the chance of getting it will be higher if a person does not urinate often¹⁴.

The use of *Orthosiphon stamineus* extract prevents the aggregation of calcium oxalate crystal by altering its surface and reducing crystal size. The development of the crystal is inhibited by the reduction in retention time via diuresis with increasing potassium elimination. Moreover, spontaneous voiding of kidney's stones less than five



millimeters is also induced. The herbal extract impresses the uric acid level and decreases it by blocking its production¹⁵. Calcium oxalate stones constitute about 75% of renal stones while 25% correlate with uric acid stones¹⁶.

Due to the considerable levels of flavonoids and minerals in "MisaiKucing" extract; the inhibition of kidney stones is reasonable. The prevention of the crystals development and aggregation is related to the flavonoids in the herbal extract while the minerals can aid in the formation of crystals of oxalate, uric or phosphate salts. Therefore, the presence of promoters "minerals" as a former element of the oxalate salt and the inhibitors "flavonoids" are requisite and important to control the development and the growth of the mentioned salt crystals¹⁷.

Likewise, Beaux *et al*¹⁸ proven that the diuretic impact of this plant extract helps to prevent the development of the kidney stone via the boost in urine flow which diminish static urine retention in the kidneys and urine bladder.

The diuretic impact are partially related to the high content of potassium in the leaves and the existence of inositol (and probably saponins), as well as to the isolated flavones sinensetin and 3'-hydroxy-5,6,7,4'-tetramethoxyflavone which present a diuretic activity in rats after intravenous administration of 10mg / kg body weight of "MisaiKucing" extract¹⁹.

It is credible that *Orthosiphon stamineus* extract aids in the inhibition of the kidney stones development. Even though, the extract has a diuretic effect by nature, the level of potassium in the body will be decreased to a depleting level as a consequence of the high concentration of "MisaiKucing" mineral that is around 600 – 700mg per 100g of fresh leaves¹⁹.

High Blood Pressure

Blood pressure is described as the force exerted by circulating the blood in veins and arteries as it circulates through the circulatory system of the body²⁰. There are two categories of the blood pressure measurements, Systolic pressure (the top number) which reflects the beating phase and pump the blood through the arteries while diastolic pressure (the bottom number) indicates the relaxation phase of the heart^{21, 22}. The normal ratio of the blood pressure is about 120\80 (systolic\diastolic). Hypertension or High blood pressure is known as the event when the ratio of systolic\diastolic be over than 140 \90 in at least three different readings²³.

The ability of "MisaiKucing" extract is noted in decreasing the blood pressure of individuals with hypertensive and it has been used as traditional drug for long time. Ohashi *et al*²⁴ concluded that the extraction of this plant leaves was separated into a mixture of water and chloroform. It was observed that the portion of chloroform-soluble exhibit an inhibitory effect on the contractile responses on rat smooth muscle. Thirteen compounds were produced by the chloroform-soluble. Methylripariochromene (A), the main constituent found in the water portion shows a

continuous decrease in systolic blood pressure among the other compounds that are present. This approval of the ability of *Orthosiphon stamineus* extract in reducing the blood pressure of rats certainly can be applied in humans as well.

Lopes *et al*²⁵ found that the diet which is rich in antioxidants can downgrade the blood pressure in obese hypertensive while thin normotensives are not. The decline in blood pressure corresponds to the increase of Total Antioxidant Capacity (TAC) of the blood plasma in obese hypertensive during the High Antioxidant (HAO) diet. The changes in the dietary cations levels of the urine did not have a significant alteration of respondents with risk factor cluster (OHT). These findings increase the possibility of the dietary habits to stop hypertension (DASH). Diet has a critical action in reducing the blood pressure in high-risk subjects through an antioxidant activity. Based on Akowuah *et al*²⁶, the *Orthosiphon stamineus* extracts are primary antioxidants and free radical inhibitors due to the higher concentration of caffeic acid derivatives, especially rosmarinic acid (RA).

According to Beaux *et al*¹⁸, the rats that had been fed with the *Orthosiphon stamineus* extract and *Sambucus nigra* showed increasing sodium excretion in the urine. Hypertension is correlated with high level of salt intake. Therefore, the excess amounts of sodium excretion through the urine are clearly a way to scale down the blood pressure of the hypertensive patients.

In addition, Lopes *et al*²⁵ noticed that the herbal extract contained high amount of polyphenols which is considered as very good source of antioxidants in lowering the blood pressure and it's not attributed by its diuretic capability but mostly related to its antioxidant content.

Diabetes

Diabetes is considered as the high level of blood glucose due to the deficiency of insulin production or the lack of using the hormone effectively. As time goes, this imbalance of blood sugar can give rise to heart disease, vision loss, kidney disease, nerve damage and numerous complications. Diabetes is divided into two categories. First, insulin-dependent diabetes (type 1) which is the less common type and typically appears before the age of 30 years. Non-insulin-dependent diabetes (type 2) which has the higher rate of occurrence, approximately 90% of cases, normally develops after the age of 40²⁷. Mariam *et al*²⁸ explained the hypoglycaemic affect in normal rats treated orally with extract of *Orthosiphon stamineus* (1.0g / kg of body weight). This treatment led to hyperglycaemic influence inhibition.

Over all, the *Orthosiphon stamineus* aqueous extract possessed some hypoglycaemic activities which decrease the level of blood sugar. From a couple of testimonials obtained from (Nusa HerbaSdn. Bhd.) who consume this herb in the form of tablets or tea drinking said that they are prone to sweat more because of the heat generation



inside the body. Some people who consume the herb had loss weight. This result indicates that some bioactive compounds have enhanced the body metabolism by utilizing the glucose to generate energy. Hence, it will help the diabetic patients indirectly by lowering blood glucose level.

CHEMICALLY OXIDATIVE COMPOUNDS

Rosmarinic acid

Rosmarinic acid is found in many plant families such as Lamiaceae and Boraginaceae family²⁹. Considered as main biological polyphenolic compound, rosmarinic acid, C18H16O8, is the most dominant constituents of rosemary, an ester of caffeic acid and lactic acid 3,4 dihidroxifenil³⁰. Rosmarinic acid was detected in the stems and leaves from *Orthosiphon stamineus*³¹ (Fig 1). The content of rosmarinic acid in the stems, branches and the whole plant was less than the leaves. Thus, the leaves are the main organ where rosmarinic acid accumulated³². Rosmarinic acid (100 or 200 mg/kg) has a significant function in the inhibition of glomerular number loss, glomerular hypertrophy, lipid peroxidation, glomerulosclerosis, creatinine and serum urea³³.

Rosmarinic acid leads to increment of the testosterone level in the blood³⁴. In addition, Rosmarinic acid prohibits the complement system, reduces the production of leukotriene B4 in human polymorphonuclear leucocytes and enhances the production of prostaglandin E2³⁰.

Many pharmacological characteristics are exhibited in rosmarinic acid such as inhibition of cyclooxygenase and of murine cell proliferative activity, prevention of oxidation of low density lipoprotein, bronchial asthma, peptic ulcer, reduction sperm motility, ischaemic heart disease, cataract, cancer and anti-allergic. Moreover, the medical properties of rosmarinic acid are described as antioxidant, antimicrobial, antiviral, and anti-inflammatory while the biological activity of rosmarinic acid was reported to have antibacterial, antiviral, and antioxidative. Recently, rosmarinic acid demonstrated effectiveness against HIV virus^{35,39}.

Quercetin

Categorized as a subclass of flavonol, quercetin (Fig 2) is an important dietary flavonoid which exists in food including apples, onions, broccoli and many more herbal diets⁴⁰. Quercetin was found in *Orthosiphon stamineus*⁴¹, which has many potential beneficial effects on human health. In animals, Quercetin appears to have antioxidant impacts in protecting heart, brain, and other tissues against toxic compounds, ischemia-reperfusion injury and other factors which lead to induce the oxidative stress^{42,44}. Sometimes quercetin might have a pro-antioxidant property.

A dose of quercetin (20 mg/day) to rats was helpful not only to decrease malondialdehyde concentrations, but also to reduce GSH concentrations significantly and glutathione reductase activity⁴⁵. Whereas quercetin dose

(1mg/day) had markedly increased the GSH:GSSG ratio in hepatic tissue; there was no effect on GSH:GSSG ratio in plasma or cardiac tissue, however; it reduced the GSH:GSSG ratio in cardiac mitochondria. Based on results mentioned previously, quercetin seems to have complex tissue-specific effects on aspects of antioxidant protection systems⁴².

A quercetin dose (150 mg/day) for six weeks has a critical role in reducing plasma concentrations of atherogenic oxidized LDL from human^{46, 47}. *In vitro*, quercetin is also known to possess anti-allergic influence by inhibiting the histamine which is released by mast cells and basophils^{48,49}. *In vivo*, anti-asthmatic activity was registered as one of the quercetin effects (guinea pigs)^{50,51}. Quercetin had also anti-inflammatory influences by decreasing the neutrophil and eosinophil counts as well as preventing asthmatic reactions^{52,54}.

The anticancer mechanisms of quercetin *in vitro* are attributed to the presence of antiproliferative, antioxidant, proapoptotic, cell signaling impacts, and growth factor repression with potential synergism to some chemotherapeutic agents^{55, 56}. Additionally, reversing drug resistance and re-sensitizing cancer cells to some chemotherapeutic agents were reported as significant functions of quercetin^{57, 58}. Therefore, *in vitro* Findings conclude that quercetin might possibly heighten the efficiency of some chemotherapeutic agents^{59,62}. Quercetin showed possibility to prevent the growth of cancer cell *in vivo* for animal experiments including those from breast, colon, prostate and lung cancers^{63,65}.

In humans, quercetin prevents thrombus formation and platelet aggregation with availability to balance blood pressure⁶⁶. Quercetin ameliorated endothelial role because of a single dose of quercetin (200 mg) improved nitric oxide status and condensed endothelin-1 concentrations⁶⁷.

Apart from the mentioned *in vivo* traits in animal experiments, quercetin enhances the inflammatory response which is induced by carrageenan and high-fat diet. Quercetin also reduced visceral adipose tissue TNF- α , signs of arthritis, nitric oxide production and down regulated NOS expression.^{68,71}

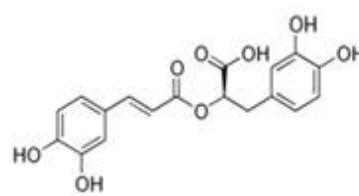


Figure 1: Rosmarinic acid⁷²

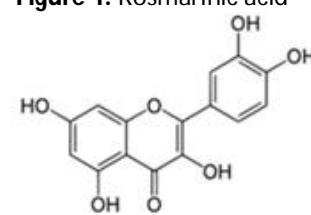


Figure 2: Quercetin⁷³

CONCLUSION

Orthosiphon stamineus is a Malaysian medicinal plant which is growing well in many countries particularly in Southeast Asia countries. This plant was reported to have secondary metabolites with biological activity properties; therefore, it has a great potential value for cultivation. In the past, many experiments have been carried out to prove the pharmacological uses of this plant, because *Orthosiphon stamineus* was known for traditional use for treating some diseases which were urinary, cardiovascular, and liver and metabolism disorder. Antioxidant, antimicrobial, antiviral and anti-inflammatory effect were shown by rosmarinic acid whereas antioxidant, anti-allergic, anticancer and anti cardiovascular activity were exhibited by querctein. We conclude that traditional use of *Orthosiphon stamineus* meets its scientific evidence in aspects of pharmacological, clinical and toxicological.

REFERENCES

1. CooperEL, Drug discovery, CAM and natural products, Evidence-Based Complementary and Alternative Medicine, 1, 2004, 215-217.
2. Firenzuoli F, Gori L, Herbal medicine today: clinical and research issues, Evidence-Based Complementary and Alternative Medicine, 4, 2007, 37-40.
3. TruongDM, Bich ThuNT, NghiLT, Accumulation and variation of rosmarinic acid content in *Orthosiphon stamineus Benth.* based on phenological stages, Journal of Biology, 32, 2012, 65-71.
4. ZakariaZ, AzizR, LachimananYL, SreenivasanS, RathinamX, PetaniS, Antioxidant activity of Coleus blumei, *Orthosiphon stamineus*, Ocimum basilicum and Mentha arvensis from Lamiaceae family, Int J Nat Eng Sci, 2, 2008, 93-95.
5. RabeT, Van StadenJ, Antibacterial activity of South African plants used for medicinal purposes, Journal of Ethnopharmacology, 56, 1997, 81-87.
6. IkawatiZ, WahyuonoS, MaeyamaK, Screening of several Indonesian medicinal plants for their inhibitory effect on histamine release from RBL-2H3 cells, Journal of ethnopharmacology, 75, 2001, 249-256.
7. AbdullahNR, Ismail Z, IsmailZ, Acute toxicity of *Orthosiphon stamineusBenth* standardized extract in Sprague Dawley rats, Phytomedicine, 16, 2009, 222-226.
8. Dixon RA, Xie DY, Sharma, SB, Proanthocyanidins—a final frontier in flavonoid research? of Article, New Phytologist, 165, 2005, 9-28.
9. Akowuh GA, Ismail Z, AhmadM, HPLC-TOF/MS profile and nitric oxide scavenging activity of *Orthosiphon stamineus*leaf extracts, Asian Pacific Journal of Tropical Biomedicine, 2, 2012, S1436-S1439.
10. Gao DF, Zhang YJ, Yang CR, Chen KK, Jiang HJ, Phenolic antioxidants from green tea produced from *Camellia taliensis*, Journal of Agricultural and Food Chemistry, 56, 2008, 7517-7521.
11. Chin JH, Abas HH, Sabariahl, Toxicity study of *Orthosiphon stamineus* Benth (Misai Kucing) on Sprague Dawley rats, Trop Biomed, 25, 2008, 9-16.
12. SriplangK, AdisakwattanaS, Rungsipipat A, Yibchok-anunS, Effects of *Orthosiphon stamineus* aqueous extract on plasma glucose concentration and lipid profile in normal and streptozotocin-induced diabetic rats, Journal of Ethnopharmacology, 109, 2007, 510-514.
13. Sheng X, Ward MD, Wesson JA, Adhesion between molecules and calcium oxalate crystals: critical interactions in kidney stone formation, J Am Chem Soc, 125, 2003, 2854-5.
14. ButterweckV, KhanSR, Herbal medicines in the management of urolithiasis: alternative or complementary?, Planta Med, 75, 2009, 1095-1103.
15. ZhongYS, YuCH, YingHZ, Wang ZY,CaiHF, Prophylactic effects of *Orthosiphon stamineus Benth.* extracts on experimental induction of calcium oxalate nephrolithiasis in rats, Journal of Ethnopharmacology, 144, 2012, 761-767.
16. Wesson JA, Johnson RJ, Mazzali M, Beshensky AM, Stietz S, Giachelli C, Liaw L, Alpers CE, Couser WG, Kleinman JG, HughesJ, Osteopontin is a critical inhibitor of calcium oxalate crystal formation and retention in renal tubules, J Am Soc Nephrol, 14, 2003, 139-147.
17. AbdullahS, ShaariAR, AzimiA, Effect of Drying Methods on Metabolites Composition of Misai Kucing (*Orthosiphon stamineus*) Leaves, APCBEE Procedia, 2, 2012, 178-182.
18. BeauxD, FleurentinJ, Mortier F, Effect of extracts of *Orthosiphon stamineus benth*, Hieracium pilosella L., Sambucus nigra L. and Arctostaphylos uva-ursi (L.) spreng. in rats, Phytotherapy Research, 12, 1998, 498-501.
19. Anon, *Orthosiphon* Medicinal and Poisonous Plants, Leiden: Buckhuys Publication, 2001, pp. 368-371.
20. Klabunde RE, Normal and Abnormal Blood Pressure (Physiology, Pathophysiology & Treatment), Kindle edition, 2013, 134.
21. Coleman A, Freeman P, Steel S, Shennan A, Validation of the Omron 705IT (HEM-759-E) oscillometric blood pressure monitoring device according to the British Hypertension Society protocol, Blood pressure monitoring, 11, 2006, 27-32.
22. El AssaadMA, TopouchianJA, Asmar RG, Evaluation of two devices for self-measurement of blood pressure according to the international protocol: the Omron M5-I and the Omron 705IT, Blood pressure monitoring, 8, 2003, 127-133.
23. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, GermanoG, Grassi G, HeagertyAM, KjeldsenSE, LaurentS, NarkiewiczK, Ruilope L, Rynkiewicz A, Schmieder RE, BoudierHAJS, Zanchetti A, 2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension, Journal of Hypertension, 25, 2007, 1751-1762.
24. OhashiK, BohgakiT, Shibuya H, Antihypertensive substance in the leaves of kumis kucing (*Orthosiphon aristatus*) in Java island, Yakugaku Zasshi, 120, 2000, 474-482.
25. Lopes HF, Walle T, Nashar K, Egan BM, P-246: Total antioxidant capacity, an important factor affecting blood pressure responses to diet?, American Journal of Hypertension, 15, 2002, 119A.
26. AkowuhGA, IsmailZ, NorhayatiI, SadikunA, The effects of different extraction solvents of varying polarities on polyphenols of *Orthosiphon stamineus* and evaluation of the free radical-scavenging activity, Food Chemistry, 93, 2005, 311-317.
27. WilkinT, The accelerator hypothesis: weight gain as the missing link between type I and type II diabetes, Diabetologia, 44, 2001, 914-922.
28. MariamA, AsmawiMZ, SadikunA, Hypoglycaemic activity of the aqueous extract of *Orthosiphon stamineus*, Fitoterapia, 67, 1996, 465-468.
29. BandonieneD, Murkovic M, Venskutonis PR, Determination of rosmarinic acid in sage and borage leaves by high-performance liquid chromatography with different detection methods, Journal of Chromatographic Science, 43, 2005, 372-376.
30. Ferreira LG, Celotto AC, CapelliniVK, Albuquerque AAS, de Nadai T, de Carvalho MTM, EvoraPRB, Does rosmarinic acid underestimate



- as an experimental cardiovascular drug?, *Acta Cirurgica Brasileira*, 28, 2013, 83-87.
31. Koay YC, Amir FA, survey of the chemical constituents and biological activities of *orthosiphon stamineus*, *Sci. Int.*, 24, 2012, 133-138.
 32. Akowuah GA, Ismail Z, Ahmad M, HPLC-TOF/MS profile and nitric oxide scavenging activity of *Orthosiphon stamineus* leaf extracts, *Asian Pacific Journal of Tropical Biomedicine*, 2, 2012, 1436-1439.
 33. Tavafi M, Ahmadvand H, Khalatbari A, Tamjidipoor A, Rosmarinic acid ameliorates diabetic nephropathy in uninephrectomized diabetic rats, *Iranian Journal of Basic Medical Sciences*, 14, 2011, 275-283.
 34. Farsi A, Khaki A, Fathiazad F, Afshari F, Hajhossini L, Kahki AA, Improvement Effect of Rosmarinic Acid on Serum Testosterone Level after Exposing with Electromagnetic Fields, *international journal of women's health and reproduction sciences*, 1, 2013, 46-50.
 35. Petersen M, Simmonds MSJ, Rosmarinic acid, *Phytochemistry*, 62, 2003, 121-125.
 36. ParkSU, Uddin MR, Xu H, Kim YK, Lee SY, Biotechnological applications for rosmarinic acid production in plant, *African Journal of Biotechnology*, 7, 2008, 4959-4965.
 37. SahibHB, Ismail Z, Othman NH, Abdul MajidAMS, *Orthosiphon stamineus Benth.* Methanolic extract enhances the anti-proliferative effects of tamoxifen on human hormone dependent breast cancer, *International Journal of Pharmacology*, 5, 2009, 273-276.
 38. Al-Sereiti MR, Abu-Amer KM, Sen P, Pharmacology of rosemary (*Rosmarinus officinalis* Linn.) and its therapeutic potentials, *Indian Journal of Experimental Biology*, 37, 1999, 124-130.
 39. Ellis BE, Towers GH, Biogenesis of rosmarinic acid in *Mentha*, *Biochemical Journal*, 118, 1970, 291-297.
 40. Middleton E Jr, Effect of plant flavonoids on immune and inflammatory cell function, *System advances in experimental Medicine and Biology*, 439, 1998, 175-182
 41. AlshawishMA, AbdullaMA, IsmailS, AminZA, Hepatoprotective effects of *Orthosiphon stamineus* extract on thioacetamide-induced liver cirrhosis in rats, *Evidence-based Complementary and Alternative Medicine*, 2011, 6.
 42. MeyersKJ, Rudolf JL, MitchellAE, Influence of dietary quercetin on glutathione redox status in mice, *Journal of Agricultural and Food Chemistry*, 56, 2008, 830-836.
 43. AnnapurnaA, ReddyCS, Akondi RB, RaoSRC, Cardioprotective actions of two bioflavonoids, quercetin and rutin, in experimental myocardial infarction in both normal and streptozotocin-induced type I diabetic rats, *Journal of Pharmacy and Pharmacology*, 61, 2009, 1365-1374.
 44. YaoY, Han DD, Zhang T, YangZ, Quercetin improves cognitive deficits in rats with chronic cerebral ischemia and inhibits voltage-dependent sodium channels in hippocampal CA1 pyramidal neurons, *Phytotherapy Research*, 24, 2010, 136-140.
 45. ChoiEJ, Lee BH, Lee K, Chee KM, Long-term combined administration of quercetin and daidzein inhibits quercetin-induced suppression of glutathione antioxidant defenses, *Food and Chemical Toxicology*, 43, 2005, 793-798.
 46. Egert S, Bosy-Westphal A, Seiberl J, Kürbitz C, Settler U, Plachta-Danielzik S, Wagner AE, Frank J, Schrezenmeir J, RimbachG, Wolffram S, MüllerMJ, Quercetin reduces systolic blood pressure and plasma oxidised low-density lipoprotein concentrations in overweight subjects with a high-cardiovascular disease risk phenotype: A double-blinded, placebo-controlled cross-over study, *British Journal of Nutrition*, 102, 2009, 1065-1074.
 47. EgertS, Boesch-Saadatmandi C, Wolffram S, Rimbach G, Müller MJ, Serum lipid and blood pressure responses to quercetin vary in overweight patients by apolipoprotein E genotype, *Journal of Nutrition*, 140, 2010, 278-284.
 48. BronnerC, Landry Y, Kinetics of the inhibitory effect of flavonoids on histamine secretion from mast cells, *Agents and Actions*, 16, 1985, 147-151.
 49. FoxCC, Wolf EJ, Kagey-SobotkaA, Lichtenstein LM, Comparison of human lung and intestinal mast cells, *Journal of Allergy and Clinical Immunology*, 81, 1988, 89-94.
 50. JoskovaM, Franova S, Sadlonova V, Acute bronchodilator effect of quercetin in experimental allergic asthma, *Bratislava Medical Journal*, 112, 2011, 9-12.
 51. Moon H, ChoiHH, Lee JY, Moon HJ, Sim SS, Kim CJ, Quercetin inhalation inhibits the asthmatic responses by exposure to aerosolized-ovalbumin in conscious guinea-pigs, *Archives of Pharmacal Research*, 31, 2008, 771-778.
 52. Rogerio AP, Dora CL, Andrade EL, Chaves JS, Silva LFC, Lemos-SennaE, CalixtoJB, Anti-inflammatory effect of quercetin-loaded microemulsion in the airways allergic inflammatory model in mice, *Pharmacological Research*, 61, 2010, 288-297.
 53. RogerioAP, Kanashiro A, FontanariC, Da Silva EVG, Lucisano-Valim YM, Soares EG, FaccioliLH, Anti-inflammatory activity of quercetin and isoquercitrin in experimental murine allergic asthma, *Inflammation Research*, 56, 2007, 402-408.
 54. ParkHj, LeeCM, JungID, Lee JS, Jeong Yi, Chang JH, Chun SH, Kim MJ, Choi IW, Ahn SC, ShinYK, YeomSR, Park YM, Quercetin regulates Th1/Th2 balance in a murine model of asthma, *International Immunopharmacology*, 9, 2009, 261-267.
 55. AalinkeelR, Bindukumar B, ReynoldsJL, SykesDE, Mahajan SD, ChadhaKC, SchwartzSA, The dietary bioflavonoid, quercetin, selectively induces apoptosis of prostate cancer cells by down-regulating the expression of heat shock protein 90, *Prostate*, 68, 2008, 1773-1789.
 56. ZhouW, KallifatidisG, BaumannB, RauschV, MatternJ, GladkichJ, GieseN, MoldenhauerG, Wirth T, BüchlerMW, SalnikovAV, Herr I, Dietary polyphenol quercetin targets pancreatic cancer stem cells, *International Journal of Oncology*, 37, 2010, 551-561.
 57. Chen C, Zhou J, Ji C, Quercetin: A potential drug to reverse multidrug resistance, *Life Sciences*, 87, 2010, 333-338.
 58. Thangasamy T, Sittadjody S, Mitchell GC, Mendoza EE, Radhakrishnan VM, Limesand KH, Burd R, Quercetin abrogates chemoresistance in melanoma cells by modulating ΔNp73, *BMC Cancer*, 10, 2010, 282-292.
 59. ScambiaG, RanellettiFO, Panici PB, PiantelliM, BonannoG, De VincenzoR, Ferrandina G, Maggiano N, Capelli A, MancusoS, Inhibitory effect of quercetin on primary ovarian and endometrial cancers and synergistic activity with cis-diamminedichloroplatinum(II), *Gynecologic Oncology*, 45, 1992, 13-19.
 60. ScambiaG, Ranelletti FO, Benedetti Panici P, Bonanno G, De VincenzoR, Piantelli M, MancusoS, Synergistic antiproliferative activity of quercetin and cisplatin on ovarian cancer cell growth, *Anti-cancer drugs*, 1, 1990, 45-48.
 61. Akbas SH, Timur M, Ozben T, The effect of quercetin on topotecan cytotoxicity in MCF-7 and MDA-MB 231 human breast cancer cells, *Journal of Surgical Research*, 125, 2005, 49-55.
 62. Albert YenY, HerenyiovaM, WeberG, Quercetin: Synergistic action with carboxyamidotriazole in human breast carcinoma cells, *Life Sciences*, 57, 1995, 1285-1292.
 63. CastilloMH, PerkinsE, Campbell JH, Doerr R, Hassett JM, KandaswamiC, MiddletonE, The effects of the bioflavonoid quercetin on squamous cell carcinoma of head and neck origin, *The American Journal of Surgery*, 158, 1989, 351-355.



64. YangK, LamprechtSA, LiuY, Shinozaki H, Fan K, Leung D, NewmarkH, SteeleVE, Kelloff GJ, LipkinM, Chemoprevention studies of the flavonoids quercetin and rutin in normal and azoxymethane-treated mouse colon, *Carcinogenesis*, 21, 2000, 1655-1660.
65. PlakasSM, LeeTC, WolkeRE, Absence of overt toxicity from feeding the flavonol, quercetin, to rainbow trout. (*Salmo gairdneri*), *Food and Chemical Toxicology*, 23, 1985, 1077-1080.
66. Hubbard GP, Wolfgram S, Lovegrove JA, Gibbins JM, Ingestion of quercetin inhibits platelet aggregation and essential components of the collagen-stimulated platelet activation pathway in humans, *Journal of Thrombosis and Haemostasis*, 2, 2004, 2138-2145.
67. LokeWM, HodgsonJM, ProudfootJM, McKinley AJ, Pudsey IB, Croft KD, Pure dietary flavonoids quercetin and (-)-epicatechin augment nitric oxide products and reduce endothelin-1 acutely in healthy men, *American Journal of Clinical Nutrition*, 88, 2008, 1018-1025.
68. Morikawa K, Nonaka M, Narahara M, Torii I, Kawaguchi K, Yoshikawa T, Kumazawa Y, Morikawa S, Inhibitory effect of quercetin on carrageenan-induced inflammation in rats, *Life Sciences*, 74, 2003, 709-721.
69. StewartLK, Soileau JL, Ribnick D, Wang ZQ, Raskin I, Poulev A, Majewski M, Cefalu WT, Gettys TW, Quercetin transiently increases energy expenditure but persistently decreases circulating markers of inflammation in C57BL/6J mice fed a high-fat diet, *Metabolism: Clinical and Experimental*, 57, 2008, 39-46.
70. RiveraL, MorónR, SánchezM, Zarzuelo A, Galisteo M, Quercetin ameliorates metabolic syndrome and improves the inflammatory status in obese Zucker rats, *Obesity*, 16, 2008, 2081-2087.
71. Mamani-MatsudaM, Kauss T, Al-KharratA, RambertJ, FawazF, ThioliatD, MoynetD, CovesS, MalvyD, MossalayiMD, Therapeutic and preventive properties of quercetin in experimental arthritis correlate with decreased macrophage inflammatory mediators, *Biochemical Pharmacology*, 72, 2006, 1304-1310.
72. Liu J, WanY, ZhaoZ, ChenH, Determination of the content of rosmarinic acid by HPLC and analytical comparison of volatile constituents by GC-MS in different parts of *Perilla frutescens* (L.) Britt, *Chemistry Central Journal*, 7, 2013, 61.
73. MoskaugJ, CarlsenH, MyhrstadM, BlomhoffR, Molecular imaging of the biological effects of quercetin and quercetin-rich foods, *Mechanisms of Ageing and Development*, 125, 2004, 315-324.

Source of Support: Nil, **Conflict of Interest:** None.

