



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

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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 ORTHOSIPHON 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 dihydroxifenil³⁰. 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}

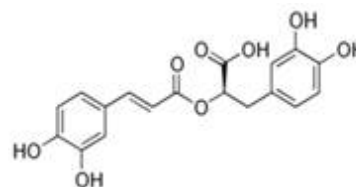


Figure 1: Rosmarinic acid⁷²

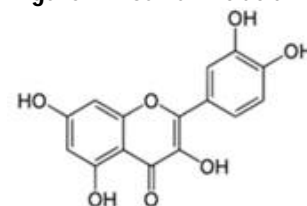


Figure 2: Quercetin⁷³

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 quercetin. We conclude that traditional use of *Orthosiphon stamineus* meets its scientific evidence in aspects of pharmacological, clinical and toxicological.

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