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Review

Phytochemistry and pharmacological properties of *Ruta graveolens* L.

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***Ruta graveolens* is known as Rue. *R. graveolens* extracts and essential oil are important areas in drug development with numerous pharmacological activities in many countries. For a long time *R. graveolens* has been used in traditional medicines for the relief of pain, eye problems, rheumatism and dermatitis. *R. graveolens* has recently been shown to have antibacterial, analgesic, anti-inflammatory, antidiabetic and insecticidal activities. Rutin, quercetin, psoralen, methoxypsoralen, rutacridone, rutacridone epoxide and gravacridondiol are phytochemical compounds which are reported from this plant. α-Pinene, limonene and 1,8-cineole were identified as the main monoterpene constituents for *R. graveolens* essential oil. Due to the easy collection of the plant and being widespread and also remarkable biological activities, this plant has become medicine in many countries especially in Mediterranean region. This article presents comprehensive analyzed information on the botanical, chemical and pharmacological aspects of *R. graveolens*.**

Key words: *Ruta graveolens*, Rutaceae, pharmacology, phytochemistry.

INTRODUCTION

Ruta graveolens L. commonly known as Rue is an herbaceous perennial, originally native to the Mediterranean region. It is now cultivated in many parts of the world. Rue has been among the key plants of the European pharmacopoeia since ancient times. Its virtues were recognized by some of the greatest Greek and Roman authors including Hippocrates, Dioscorides and Pliny (Miguel, 2003). There are two main species used in traditional medicine of which *R. graveolens* is more important (Ratheesh and Helen, 2007). It belongs to Rutaceae family in the order of Sapindales that contains about 160 genera and more than 1600 species. Due to its cultural and medicinal value, rue has been introduced in various countries of North, Central and South America, China, India, Middle East and South Africa (Miguel, 2003). *R. graveolens* has been known as “Sodaab” in Iran and distributed in northern parts of Iran especially in Gilan Province (Naghibi Harat et al., 2008). *R. graveolens* is a small evergreen sub-shrub or semi woody perennial 0.6 to 0.9 m tall and almost as wide. The stems become woody near the base, but remain herbaceous nearer the tips (Figure 1). The 7.6 to 12.7 cm long leaves are dissected pinnately into oblong or spoon shaped segments. They are somewhat fleshy and usually covered with a powdery bloom (Figure 2). The sea green foliage has a strong, pungent, rather unpleasant scent when bruised. The paniculate clusters of small yellow flowers appear in midsummer, held well above the foliage and often covering most of the plant. Each flower is about 1.3 cm across with four concave notched petals (Figure 3) (Zargari, 1988).

Extracts from *R. graveolens* have been used as an antidote for toxins such as snake and scorpion venoms (Sallal and Alkofahi, 1996).

For a long time, *R. graveolens* has been used as a folklore medicine for treatment of various conditions such as eye problems, rheumatism, dermatitis, pain and many inflammatory diseases (Ratheesh and Helen, 2007). It acts as an emenagogue through the effect of rutin and stimulates the uterine basal fiber (Miguel, 2003). It was not recommended for use by pregnant or lactating

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Figure 1. *Ruta graveolens* (Rue).

Figure 2. *R. graveolens* leaves.

Figure 3. *R. graveolens* flower.

women because in high concentrations it can provoke hyperemia in the uterus and high mobility (oxytocic action) which may cause abortion. At the concentrations needed for this effect, it can cause the death of a pregnant woman. *R. graveolens* is rich in rutin which act as a venotonic and capillary protector. Rutin helps increase visual sharpness and benefits other visual problems, and it was used against edema, thrombo-genesis, inflammation, spasms, and hypertension (Miguel, 2003). The essential oil is spasmolytic, anti-inflammatory and antihistaminic and is a vermifuge (Mansour et al. 1989). *R. graveolens* can also be used as a rubefacient, applied in poultices for rheumatic pain, dislocations, tendon strains, varicose veins and skin conditions such as psoriasis and eczema. It has bitter eupeptic properties, so it is prescribed for stomach and intestinal disorders. If externally spread on moist skin under direct sunlight it leads to photosensitivity, caused by furanocoumarins resulting in hyper pigmentation, swelling, itching, and even burns and blistering (Miguel, 2003).

The essential oil also has a depressing effect on the central nervous system. At high doses it works as a narcotic poison, provoking violent intestinal inflammation, tongue and larynx tumefaction, excitement, followed by fatigue, vertigo, mental confusion, trembling, nephritis with uterine swelling and abortion, liver damage, intestine damage, and eventually death (Miguel, 2003).

A number of chemical constituents such as alkaloids, coumarins, volatile substances, terpenoids, flavonoids and furoquinolines have been isolated from different parts of the plant (kuzovkina et al., 2004).

From current pharmaceutical studies, additional pharmaceutical applications of *R. graveolens* have revealed antioxidant, anti-inflammatory (Ratheesh and Helen, 2007), antidiabetic (Toserkani et al., 2011), antibacterial, antifungal (Meepagala et al., 2005), antiandrogenic(Khouri and El-Akawi, 2005), insecticide (Barbosa et al., 2011), effects among others.

Since review and systemic analysis of chemistry, pharmacology and clinical properties of *R. graveolens* have not been reported, we prompted to provide the currently available information on traditional and local knowledge, ethno biological and ethno medicinal issues, identification of pharmacologically important molecules and pharmacological studies on this useful plant. The aim of this article is to introduce *R. graveolens* as a potent medicinal plant by highlighting its traditional applications as well as the recent findings for novel pharmacological and clinical applications.

CHEMICAL COMPOSITION

The commonly known phytochemical compounds from *R. graveolens* are acridone alkaloids, coumarins, volatile substances, terpenoids, flavonoids and furoquinolines (kuzovkina et al., 2004). The existence of saponin,

tannins and glycosides has also been proven (Hashemi et al., 2011). Rutin and quercetin are the main active flavonoids of *R. graveolens.* Rutin was first isolated from the leaves of *R. graveolens* (Pathak et al., 2003). A high content of aliphatic acids, alcohols and ketons were found in *R. graveolens* volatile oil (Ivanovaa et al., 2003). 2-undecanone (33.9%), 2-Heptanol acetate (17.5%),1-dodecanol (11.0%), geyrene (10.4%), 2-nonanone (8.8%), 2-Decanone (1.9%), Geijerene (1.6%), trans-piperitenone oxide (1.4%), cis-piperitenone oxide (1.2%), 2-methyl-undecanal (1.1%), 2-dodecanone (1.1%), 2-nonanol (1.1%), elemol (1.1%) are the main components of the essential oil of the flowering aerial parts of the plant (Soleimani et al., 2009). *R. graveolens* produces high levels of linear furanocoumarins, mostly psoralen and methoxypsoralen (Gravot et al., 2004).

Rutacridone, rutacridone epoxide and gravacridondiol are acridone alkaloids isolated from *R. graveolens* root (Meepagala et al., 2005) while an alkaloid named graveoline has been isolated from the leaves (Hale et al., 2004) (Figure 4).

POTENTIAL OF *R. GRAVEOLENS* IN PHYTOTHERAPIES

According to the literature (Ahmed et al., 2010), *R. graveolens* contains approximately 2% of rutin which is the main flavonoid of the plant. Flavonoids, and particularly quercetin derivatives, have received special attention as dietary constituents in the last few years. Epidemiological studies have pointed out their possible role in preventing cardiovascular disease and cancer (Hertog et al, 1992; Kamalakkannan and Prince, 2006). This health-promoting activity seems to be related to the antioxidant (free-radical scavenging) activity to flavonoids (Murota and Terao, 2003). Quercetin is one of the most common native flavonoids occurring mainly in glycosidic forms such as rutin (Muroat and Terao, 2003; Havsteen, 1983). Rutin exhibits multiple pharmacological activities including antibacterial, antitumor, antiinflammatory, antidiarrheal, antiulcer, antimutagenic, myocardial protecting, vasodilator, immunomodulator and hepatoprotective activities (Janbaz et al., 2002).

ANTI-INFLAMMATORY AND ANALGESIC PROPERTIES

Although a number of steroidal or non-steroidal anti-inflammatory drugs have been developed, researchers are changing their focus to natural products to develop new anti-inflammatory agents due to the side-effects of chemical drugs (Hyun and Kim, 2009; Shokrzadeh and Saeedi Sarvari, 2009). As a result, the search for other alternatives seems necessary and beneficial. *R. graveolens* is an open door for new and effective compounds. Many cells and mediators are involved in proceeding inflammation. For example, macrophages are representative inflammatory cells involved in acute or chronic inflammatory responses by over-production of pro-inflammatory cytokines [for example, tumor necrosis factor (TNF)-a, interleukin (IL)-1b and granulocyte/ macrophage colony stimulating factor (GMCSF)] and inflammatory mediators (Rhee et al., 2009; Lundberg, 2003; Walsh, 2003). The aerial parts of *R. graveolens* have been functionally used as a traditional crude drug as a poultice against rheumatic pain (Ratheesh and Helen, 2007). In animal models, ethanolic and methanolic extracts of *Ruta graveolens* with a concentration of 20 mg/kg and ethanolic extract with a concentration of 50 mg/kg showed maximum (90.9%) inhibition on carrageenan induced rat paw edema. The effect was significantly ($P< 0.05$) higher than that of the standard drug Voveran (72.72%). Methanol extract with a concentration of 50 mg/kg b.w. produced 81.81% inhibition, which was also high as compared to the standard drug. Ethanolic extract with a dose of 20 mg/kg and the two doses of aqueous extract produce less percentage of inhibition as compared to the standard drug Voveran (Ratheesh and Helen, 2007).

The development of edema in the paw of the rat after the injection of carrageenan is due to release of histamine, serotonin and prostaglandin like substances (Vinegar et al., 1969). Significantly high anti-inflammatory activity of methanolic and ethanolic extracts of *R. graveolens* may be due to inhibition of the mediators of inflammation such as histamine, serotonin and prostaglandin (Ratheesh and Helen, 2007).

The methanolic extract of *R. graveolens* markedly reduces cell influx, edema, release of mediators and oxidative stress associated with arthritic condition, and therefore has the potential to be used as an anti-arthritic agent. These effects may be due to the presence of the broad range of flavonoids present in the plant extract especially rutin and quercetin (Ratheesh et al., 2009).

Antinociceptive profiles of *R. graveolens* extract were also examined in mice. Orally administration of the extract (200 mg/kg) showed an antinociceptive effect as measured by the tail-flick and hot-plate tests and attenuated the writhing numbers in the acetic acid-induced writhing test. *R. graveolens* had a significant antinociceptive effect and this activity may be mediated by opioidergic and α2-adrenergic receptors, but not by serotonergic receptors (Park et al., 2010).

ANTIANDROGENIC ACTIVITY

R. graveolens is currently used by many people in Jordan as an aphrodisiac and fertility promoting agent. The investigations have clearly shown that oral administration of *R. graveolens* promoted a decreased male albino rat's fertility. It is well known that the weight, size and the secretory function of testes, epididymes, seminal vesicles, ventral prostate are closely regulated by

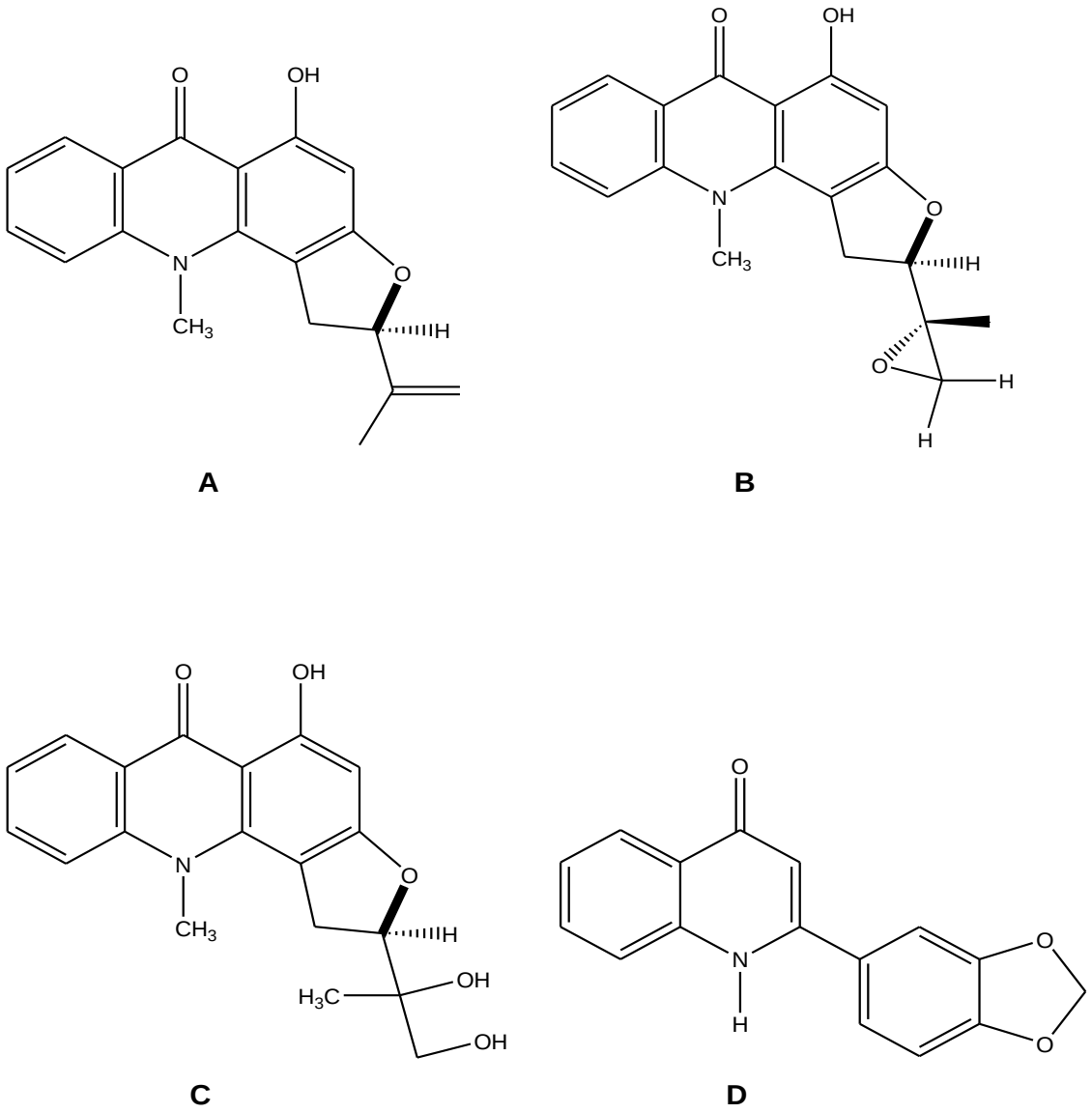

Figure 4. Structures of A= Rutacridone; B= Rutacridone epoxide; C= Gravacridondiol; D= Graveoline; from *R. graveolens* (Meepagala et al., 2005; Hale et al., 2004).

androgens hormones (Choudhary and Steinberger, 1975). *R. graveolens* extract may act directly or indirectly on the pituitary gland secretory function leading to an increase in the main hormones controlling spermatogenesis process. It has been demonstrated that the process of spermatogenesis and the accessory reproductive organs function are androgen dependent. Therefore, changes in the androgen production would reflect and explain the decrease in number of mature Leydig cells and their functional status. *R. graveolens* extract significantly decreased the number of degenerating Leydig cells that lead to a decrease in the serum androgen level. A decrease in number of spermatocytes and spermatids and in the sperm motility was also observed. The results indicated that ingestion of *R. graveolens* by adult male rats reduces the number of females' impregnation. In addition, the number of implantations and the number of viable fetuses were decreased. This decreased could be reflecting and may be due to the decrease in sperm motility and sperm density. This may be due to the activity effects of *R. graveolens* on the enzymes involved in the oxidative phosphorylation process (khouri et al., 2005).

R. graveolens also stimulates muscles of the uterus, which in turn may initiate menstrual cycles. It decreases fertility and may also block the implantation of a fertilized egg. The results showed a significant decrease in the number of primordial follicles. Also the ovarian weight, number of corpus luteum and the diameter of remaining corpus luteum decreased. The number of atretic graffian

follicles was significantly increased ($p<0.05$), while estrogen levels were significantly decreased (khouri et al., 2005).

Aqueous extract of R. graveolens can interfere with reproductive system function in immature female mice by alterations in sex hormonal level and ovarian morphology and might be useful as an antifertility substance (Nasirinezhad et al., 1997).

ANTIHYPERGLYCEMIC EFFECTS

It has been found that the treatment of diabetic rats with either *R. graveolens* infusion or its flavonoid, rutin, lead to significant amelioration of glucose tolerance. The hypoglycemic effect of *R. graveolens* may be due to the presence of flavonoids such as rutin. Serum insulin concentration was increased markedly as a result of treating diabetic rats with both *R. graveolens* and rutin. By its ability to scavenge free radicals and to inhibit lipid peroxidation (Liao and Yin, 2000), rutin prevents STZ-induced oxidative stress, protects β-cells resulting in increased insulin secretion, and decreases elevated blood glucose levels (Ahmed et al., 2010).

The treatment with both *R. graveolens* infusion and rutin produced a marked increase in serum C-peptide level of diabetic rats. The marked increase in serum insulin and C-peptide levels after treatment of diabetic rats with *R. graveolens* infusion and rutin was due to the stimulatory effects of these agents on the insulin secretory response of the islets of Langerhans on the one hand, in addition to the ameliorative effects of these agents on the integrity of β-cells as revealed by histologic study (Ahmed et al., 2010).

Serum fructosamine level, a putative measure of glycosylated proteins which has been suggested by many authors to be of value as a screening test for diabetes mellitus (Hindle et al., 1986; Donnelly, 1996), was profoundly increased in diabetic rats at fasting state as compared with normal ones. Rutin with its free radical scavenging capability effectively reduced the formation of glycated proteins (Ahmed et al., 2010). A decrease in blood glucose levels may have also contributed to decreased levels of glycated proteins in *R. graveolens* and rutin treated diabetic rats.

The increased hepatic glucose output in diabetes may be derived from glycogenolysis and/or gluconeogenesis (Raju et al., 2001). Results revealed an enormous depletion in hepatic glycogen content accompanied by a decreased hexokinase activity and profound elevation of hepatic glycogen phosphorylase activity and the gluconeogenic enzyme, glucose-6-phosphatase, as compared to that of normal control ones. These changes may be due to insulin deficiency and/or insulin resistance, which in turn results in the activation of glycogenolytic and gluconeogenic pathways (Abdel-Moneim et al., 2001; Ahmed, 2006). Moreover, deficiency of insulin secretion decreases hepatic tyrosine kinase responsible for the activation of glycogen synthase and as a result, glycogen breakdown prevails in diabetic animals (Bollen et al., 1998). The elevation of liver glycogen content after treatment with *R. graveolens* extract and rutin was due to amelioration of these altered enzyme activities secondary to the increase of insulin levels in the blood as well as improvement of insulin action. In addition, the enhanced peripheral glucose uptake and increased hepatic hexokinase activity as well as decreased glucose-6-phosphatase activity after treatment with the tested agents. The increase in hexokinase activity and the decrease in glucose-6-phosphatase, in the present study, may have also reflected a decrease in hepatic glucose output and enhanced peripheral glucose uptake. *R. graveolens* infusion and rutin produced a marked increase of peripheral glucose consumption in the presence and absence of insulin as compared with the corresponding controls. Both agents acted in a dose dependent manner with a more potent effect for rutin than rue infusion. The marked increase in the peripheral glucose uptake in the absence of insulin as a result of the tested agents suggests that they may have insulin mimetic action or non-insulin mediated effect. All doses of both agents were able to potentiate the enhanced effect of insulin on peripheral glucose uptake in the presence of insulin. Both *R. graveolens* and rutin increased the *in vitro* insulin binding affinity of rat diaphragm in a dose dependent manner. Thus, the insulin mediated effects of the tested agents may have included the increase in insulin binding affinity by these agents. In addition to the effect on hepatic glucose output and peripheral glucose uptake, the plant infusion and rutin induced a profound decrease in intestinal glucose absorption in a dose dependent manner (Ahmed et al., 2010).

Both *R. graveolens* and rutin improved glucose tolerance and this amelioration seemed to be mediated *via* alleviation of the islet architecture, enhancement of insulin release, insulin binding affinity and peripheral glucose uptake and decreasing intestinal glucose absorption in addition to decreasing the activity of gluconeogenic and glycogenolytic enzymes (Ahmed et al., 2010).

ANTIHYPERLIPIDEMIC EFFECTS

The reduction of intestinal cholesterol absorption might have a role in the mechanism of action to augment the hypolipidemic activity of *R. graveolens* and rutin. Furthermore, the hypolipidemic activity of both *R. graveolens* and rutin may also be mediated via inactivation of hepatic HMG-CoA reductase, a key enzyme, in cholesterol synthesis. Inhibitors of hepatic HMG-CoA reductase are well established drugs for the treatment of hypercholesterolemia and decrease the incidence of dyslipidemia in diabetic subjects

(Raz et al., 2005). Flavonoids decrease liver HMG-CoA reductase activity in type II diabetic mice. Moreover, rutin has been reported to lower hepatic and blood cholesterol levels (Park et al., 2002).

Taken together, it can be concluded that the ameliorative effect of *R. graveolens* extract or rutin on serum lipid variables may be attributed to their insulin releasing capacity and insulin binding affinity and decreasing intestinal cholesterol absorption and activity of hepatic HMG-CoA reductase (Ahmed et al., 2010).

XANTHINE OXIDASE INHIBITION ACTIVITY

Gout and hyperurecimia are metabolic disorders resulted from abnormal production and excretion of uric acid in the body (Kong et al., 2000). Xanthine oxidase (XO) is an enzyme mainly responsible for final reactions of uric acid production from oxidizing oxypurines, hypoxanthine and xanthine (Beedham, 1998; Linder et al., 2003). XO also plays an important role in the metabolism of many xenobiotics and drugs such as purines and pyrimidines (Krenitsky et al., 1986). Additionally, it has been shown that the activity of this enzyme is commonly over-expressed in ischemia-reperfusion injury and some other related clinical complications such as brain tumor, hepatitis, organ transplantations, birth trauma, and severs intense physical activity (Judge and Dodd, 2004). Therefore, the inhibition or activation of XO may result in some important therapeutic or toxic effects.

R. graveolens is an herbaceous plant, which is rich in flavonoids as its major active reagents such as rutin and quercetin. Its extract and the major isolated flavonoids, quercetin and rutin, had potent activity on guinea pig liver XO. Interestingly, XO enzyme was inhibited significantly at different ranges by either the extract or its flavonoids, whereas allopurinol acted with almost the same potency on the enzyme. Rutin inhibited the enzyme in a competitive manner, while quercetin was found to be a competitive and mixed inhibitor of XO, respectively. Therefore, *R. graveolens* extract can act as a good inhibitor of XO (Pirouzpanah et al., 2009).

ANTICANCER PROPERTIES

Ruta Q, the mother tincture extracted from *R. graveolens* according to homeopathic pharmacopia, has been diluted to Ruta 1 by adding 1 ml of Ruta Q to 99 ml of absolute ethyl alcohol. 1 ml of Ruta 1 when added to 99 ml of alcohol has made Ruta 2. Similarly, Ruta 6 has been prepared by performing more serial dilutions (Pathak et al., 2003).

It was found that a combination of Ruta 6 and $Ca_3(PO_4)_2$ taken orally can either block the progression of or completely regress human glioma brain cancers, with minimal or no side effects. The patients diagnosed with glioma, when treated with Ruta 6, showed better results compared with patients having other types of intracranial cancers (Pathak et al., 2003).

Although, ruta is cytotoxic to human and cancer cells, it is more damaging to human glioma brain cancer cells than to HL-60 leukemia cells. Ruta induces cell division in normal human PBLs but does not induce chromosome aberrations in normal B-lymphoid cells or PHA stimulated T lymphocytes. Ruta does not protect human glioma brain cancer cells from genetic damage induced by H_2O_2 while protects B-lymphoid cells from H_2O_2-inflicted damage as measured by a reduced number of metaphases with chromosome aberrations. Ruta induces severe telomere erosion in MGR1 brain cancer cells but has no effect on B-lymphoid cells and normal lymphocytes. Preferential killing of glioma brain cancer cells by Ruta is apparently mediated through the loss of telomeric DNA, followed by the arrest of cells in the G2/M phase, induction of endomitosis and fragmentation of DNA, leading to cell death. Analysis indicates that Ruta induces cell death in a dose- and duration-dependent manner in human MGR1 brain cancer cells, followed by saturation effects. However, Ruta protects B-lymphoid cells and PHA stimulated T lymphocytes, even acting as a mild mitogen in such cultures (Pathak et al., 2003).

In addition, Ruta is also known to protect from DNA strand breaks and to prevent mutagenesis (Aherne and O Brien, 2000; Bear and Teel, 2000). $Ca_3(PO_4)_2$ was added because it activates phospholipase, which cleaves phosphalidylinositol biphosphate, a membrane-bound molecule that activates protein kinase C (Pathak et al., 2003).

The cleavage product brought about by phospholipase triggers which help transfer the cytoplasmic nuclear factor of activated T cells into the nucleus via calmodulin- and calcineurin-associated enzymes. Calcineurin modulates the induction of tumor necrosis factor, a potent activator of NF- κB, which ultimately leads cells to apoptosis (Tomei and Cope, 1991; Singh and Aggarwal, 1995) and/or spontaneous regression or prolonged arrest of tumor cells (Everson and Cole, 1996). NF-κB is a transcription factor and plays a critical role in the immune system. Ruta also induces removal of an amide group of the antiapoptotic protein Bcl-xL in human brain cancer cells but not in normal B and T lymphocytes. This process is known to occur in a regulatory domain of Bcl-xL which renders inactivation of this protein. This may result in the cancer cells becoming more sensitive to cell death than normal cells (Li and Thompson, 2002).

The Ruta 6 and $Ca_3(PO_4)_2$ combination was capable of protecting normal B-lymphoid cells against H_2O_2-induced chromosome damage by reducing the level of damage >50% (Pathak et al., 2003).

Telomeres, which protect individual chromosomes and the entire genome, are reduced in Ruta 6- treated cancer cells but not in normal B-lymphoid cells. It is clear from in vivo and *in vitro* observations that Ruta has the novel property of preferentially killing human glioma brain

cancer cells and protecting normal body cells. Overall, the results show that plant-derived Ruta 6 and $Ca_3(PO_4)_2$, when taken orally, can induce regression of human glioma brain cancers in vivo. In contrast to conventional chemotherapy that kills not only cancer cells but also normal cells, the Ruta 6 + $Ca_3(PO_4)_2$ combination kills glioma brain cancer cells selectively and protects normal lymphocytes by inducing cell division in blood-forming cells (Pathak et al., 2003).

CONCLUSION

The objective of this review has been to show the recent advances in the exploration of *R. graveolens* as phytotherapy and to illustrate its potential as a therapeutic agent. With the current information, it is evident that *R. graveolens* has pharmacological functions including anti-inflammatory, analgesic, antiandrogenic, antihyperglycemia, antihyperlipidemia, anti-gout and anticancer activities, among others. As the current information shows, it is also possible that flavonoids especially rytin and quercetin, and some alkaloids might be useful in the development of new drugs to treat various diseases. However, the present results suggest a possibility that furanocoumarins can be further developed as a potential disease-curing remedy. It must be kept in mind that clinicians should remain cautious until more definitive studies demonstrate the safety, quality and efficacy of *R. graveolens*. For these reasons, extensive pharmacological and chemical experiments, together with human metabolism will be a focus for future studies. Last but not the least, this article emphasizes the potential of *R. graveolens* to be employed in new therapeutic drugs and provide the basis for future research on the application of transitional medicinal plants.

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