Websites:
http://www.sciencepub.net
http://www.sciencepub.net/stem

Emails:
editor@sciencepub.net
sciencepub@gmail.com

Stem Cell

MARSLAND PRESS
Multidisciplinary Academic Journal Publisher

Review On Medicinal Value And Side Effect Of Ruta

Betelhem Awoke (DVM), *Abraham Jemberu (DVM)

College of Veterinary Medicine, Mekelle University, Mekelle, Ethiopia, P.O. Box. 2084
Email: abrishvet@gmail.com / abrishjvmd@gmail.com

Abstract: *Ruta* popularly known as rue is a multipurpose herb belonging to family *Rutaceae* has been used as a source of food and medicine for thousands of years. It has played an important dietary as well as medicinal role in human history and it has been on the top list of herbal sales among people. Today, it is commonly used in much culture as a seasoning or spice. Therefore, this paper is designed with the objective to review the medicinal values and toxicity of *Ruta*. *Ruta* has the potential of curing a man from a large number of diseases by inhibiting the growth of different strains of bacteria, fungi, parasites; it has also insecticidal and anti-inflammation activities. The active constituents are a rich source of secondary metabolites mainly: *coumarins*, *alkaloids*, *volatile oils*, *flavonoids*, and *phenolic acids*. It has been used abundantly worldwide due to its diverse medicinal properties that are rapidly absorbed and metabolized. The composition of *Ruta* is consistent with their use as flavoring agents in food as well as their use herbal medicines. The chemical ingredients of *Ruta* species have also been found to be useful for treatments of cancer, diabetes, hyperlipidemia and cardiovascular diseases, also found to have antipyretic, antioxidant properties. Pregnant women and animals especially goat and horse are highly susceptible to *Ruta* species. A recent increase in the popularity of alternative medicine and natural products has renewed interest in *Ruta* species and their derivatives as potential natural remedies. Therefore, more studies are needed to refine the use and improvement of the efficacy of this important medicine plant.
[Betelhem Awoke, Abraham Jemberu. **Review On Medicinal Value And Side Effect Of Ruta.** *Stem Cell* 2020;11(3):45-52]. ISSN: 1945-4570 (print); ISSN: 1945-4732 (online). http://www.sciencepub.net/stem. 8. doi:10.7537/marsscj110320.08.

Key Words: *Alkaloids*, *Coumarins*, *Flavonoids*, Medicinal Value, *Ruta*, Toxicity, *Volatile Oils*

1. Introduction

Since the beginning of human civilization, medicinal plants have been used by mankind for its therapeutic value. According to the WHO in 2008, more than 80% of the world's population relied on traditional medicine due to their significant healing powers and lesser side effects (Shanazi *et al.,* 2006). Traditional herbal medicines are often deemed to be safe due to their natural origin (Wallace *et al.,* 2012).

Rutaceae is a large family of trees and shrubs predominantly tropical and subtropical family having 150-162 genera and 1500-2096 species (Scott *et al.,* 2000). *Ruta* is the richest genus of *Rutaceae* family. "*Ruta*" comes from the Greek word "*reuo*", to set free, showing its reputation as a free from disease. The genus ruta have 8 to 40 species, which is strongly scented evergreen sub shrubs having 20cm-1m tall, in the family *Rutaceae*. The leaves are bipinnate or tripinnate, with a feathery appearance, and green to strongly *glaucous* blue-green in colour (Groppo *et al.,* 2012). The flowers are yellow, with 4–5 petals, about 1 cm diameter, and bloom during spring and summer. The fruit is a 4-5 lobed capsule, containing numerous seeds originally native to the Mediterranean region but now genus *Ruta* is cultivated in many parts of the world it grows on waste stony ground (Iauk *et al.,* 2004).

Ruta species are resources of various classes of natural products with biological activities like; antifungal, antioxidant, antiviral, antidepressant, antidote and anti-inflammatory, it has been used widely in various folk medicines as analgesic and antipyretic and for treatment of mental disorders, rheumatism, and bleeding disorders (Raghav *et al.,* 2006). For a long time, *R. graveolens* has been used as a traditional medicine for treatment of various conditions such as eye problems, pain and many inflammatory diseases (Ratheesh and Helen, 2007). Extracts from *R. graveolens* have been used as antimicrobial and antifungal properties and antidote for toxins such as snake and scorpion venoms while others are medically useful (Oliva et al., 1999).

In Ethiopia, the Amharic name of *R. chalepensis L.* is Tena Adam literally means health of Adam, thus signifying the medicinal applications of the plant. In Ethiopian folk medicine it used to treat earache, hemorrhoids, *influenza* and intestinal disorders. The juice from the crushed leaves is mixed with water and

administered to colicky babies (Fullas, 2003). It is traditionally known for its abortive and anti-fever effects while *Ruta graveolens* is known for its antiparasitic, digestive, diuretic and molluscicidal activities (Boudoir et al., 2011). In addition to medicinal applications it's used for cooking and medicinal purposes. It is scientifically accepted that natural antioxidants exert health promoting effects and their consumption as food or as food additives or as nutraceuticals and supplements have been greatly promoted worldwide. A complex mixture of antioxidants may account for improvement of cardiovascular health and decreased incidence of cancer in individuals who consume more of these substances (Schmidt et al., 2015). The leaves of *Ruta chalepensis* are used commonly as spice during a traditional Ethiopian coffee and tea ceremony. The fruits are used as ingredients of the local "berbere" and "mitten shiro" spice mix. *Ruta* is a rich source of secondary metabolites mainly; *coumarins*, *alkaloids*, *volatile oils*, *flavonoids*, and *Miscellaneous* Compounds (Prabhu *et al.,* 2014).

Therefore, the objectives of this seminar paper are:

- To review the chemical compositions and medicinal value of *Ruta*.
- To describe the toxic effects of *Ruta*.

2. Chemical Composition Of Ruta

In *Ruta* species more than 120 compounds have been identified up to now. Environmental pollution, especially with heavy metals, poses serious problem on the quality of medicinal plants and their products. Thus, the element content assessment is important for specifying the relevance of application to produce drugs, *Ruta* species are rich source of secondary metabolites mainly: *Coumarins, alkaloids, volatile oils, flavonoids, and phenolic acids* (Hammiche *et al.,* 2013).

2.1. Coumarins

The main types of *Coumarins* identified in Ruta species are: simple *Coumarins, furanocoumarin, dihydrofuranocoumarins,* and *isocoumarins* among others (Hussain *et al.,* 2012). Simple coumarins isolated from the roots of the *Ruta* species for the first time were *gravelliferone methyl ether, chalepensin, daphnoetin,* and *gravelliferone.* The *furanocoumarins* with linear structure are produced in different parts of the species; studies of field grown plants showed that *furanocoumarins* concentration was proportionally related to both the plant's phonological stages and the organs in which the substance is stored (Milesi *et al.,* 2001). Fruits accumulate higher concentrations of *furanocoumarins* followed by leaves, roots, and stems. On the leaf surface, concentrations and proportions of *furanocoumarinsas psoralens*, *Xanthotoxin*, and *bergapten* vary during aging (Zobel and Brown, 1990; byshev *et al.,* 1992).

2.2. Alkaloids

Ruta species are a valuable natural source of alkaloids which can be classified as *furoquinolines*, *Acridones, quinolines, and alkylquinolinones* (Kuzovkina *et al.,* 2004; and, Eun-Tae *et al.,* 2014). The *furoquinoline alkaloids* such as *dictamine, kokusagenin, Skimmianine,* and *fagarine* occur in different amounts on the leaves, shoots, roots, and flowers (Kostova *et al.,* 1999). *kokusagenin* and *Skimmianine* are almost equally distributed in the plant's aerial parts. *Furacridone* and *rutacridone* were the first representatives from *acridone alkaloids*, to be extracted from the roots of *R. graveolens* (Meepagala *et al.,* 2005). *Graveoline* is *alkylquinolone alkaloid* isolated from the leaves of *Ruta* species. *Graveolinine* is *quinoline alkaloids* isolated from the leaves of the species (Salib et al., 2014).

2.3. Volatile Oils

The *volatile oils* obtained from *Ruta* species fruits, leaves, roots, flowers, or stems have a yellowish color, as well as an intense and penetrating odor. They are composed mainly of oxygenated compounds (*ketones, alcohols, acetates*), *sesquiterpenes* and *monoterpenes hydrocarbons*, *aromatics hydrocarbons* (Soleimani *et al.,*2009). *Monoterpenes* and *sesquiterpenes* have been identified in this plant species include, *apinene, limonene, camphene, terpinolene, camphor, geijerene,* and *geyrene* (Haddouchi *et al.,* 2013). *Pregeijerene*, *geijereneand, sesquiterpenes* compounds are the major constituents of the essential oil from *Ruta speciesroots. Xanthotoxin* was also found in the oil extracted from aerial parts and roots of the *Ruta* species (De Feo *et al.,*2002). The composition of the essential oil is affected by climatic, seasonal, and geographic conditions, harvest period, chemotypes, and/or extraction procedure (Ferhat *et al.,*2014).

2.4. Flavonoid Glycosides and Flavonoids

Ruta species are a rich source of flavonoid glycosides, for example, rutin; a yellow pigment containing *gossypetin* 7-*methyl ether* 3-*rutinoside and gossypetin* 7-*methyl ether* has been isolated from the flowers of *Ruta* species. The leaves and flowers *Ruta* species have been reported to possess *flavonoid, quercetin, kaempferol,* and *isorhamnetin* (Saieed *et al.,* 2006).

2.5. Miscellaneous Compounds

Besides the constituents listed above, other metabolites have also been reported in *Ruta* species, such as *glycosides* and *phenolic* compounds (Chien-Chih *et al.,* 2001) Phenolic acids *gentisic acid* and *ferulic acid* were isolated from the leaves of *Rutaspecies* (Proestos *et al.,*2006)

3. Potential Health Benefits Of Ruta

3.1. Treatments of Cardiovascular Disease

Medicinal plants have been in use all over the world to treat various diseases including inflammation, heart diseases, cancer, etc. Today the large numbers of drugs in use are derived from plants, which are rich in secondary metabolites and essential oils of therapeutic importance. The important advantages claimed for therapeutic uses of medicinal plants in various ailments are their safety besides being economical, effective and their easy availability (Verma and Kumar, 2011).

Ruta Chalepensis aqueous extract treatment of hypertensive rats prevented the development of hypertension, with *alkaloids*, *flavonoids*, *coumarins*, and *sterols* detected by the qualitative phytochemical analysis. These compounds have a large variety of pharmacological actions which include; stimulation of endothelial nitric oxide synthesis and inhibition of angiotensin converting enzyme (Gunaydin and Savci, 2005).

Ruta chalepensis is a rich source of important secondary metabolites such as *furanocoumarins* and *alkaloids*. The *furanocoumarin* is responsible for the *vasodilatory* activity regulated by nitric oxide in an endothelium dependent manner. Another compound present in *R. chalepensis* is *flavonoid* which is a *diglycoside* of *quercetin* (Raghav *et al.,* 2006). It has been demonstrated that *quercetin* possess antihypertensive activity in several models of hypertension and *thrombogenesis* (Pérez-Vizcaino *et al.,* 2009). The flavonoid *rutin* is used to support and strengthen blood vessels, which reduces pressure (Chevallier,1996).

3.2. Anti-diabetic Effect

Hyperglycemic has been found that the treatment of diabetic rats with *Ruta* species of flavonoid, *rutin* lead to significant amelioration of glucose tolerance. The hypoglycemic effect of *Ruta* species may be due to the presence of flavonoids such as *rutin*. Serum insulin concentration was increased markedly as a result of treating diabetes mellitus mice with *rutin*. By its ability to scavenge free radicals and to inhibit lipid peroxidation (Liao and Yin, 2000). Rutin protects β-cells resulting in increased insulin secretion, and decreases elevated blood glucose levels in diabetic rats at fasting state as compared with normal ones (Ahmed *et al.,* 2010).

The reduction of intestinal cholesterol absorption might have a role in the mechanism of action to augment the hypolipidemic activity in diabetes mellitus mice (Raz *et al.,* 2005). The effect of *rutin* on serum lipid variables attributed to their insulin releasing capacity, insulin binding affinity and decreasing intestinal cholesterol absorption (Ahmed *et al.,* 2010).

3.3. Anti-Inflammatory 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). As a result, the search for other alternatives seems necessary and beneficial so, ruta is an open door for new and effective compounds. 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, *methanolic extracts* of *Ruta* species 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 higher than that of the standard drug *Voveran* (72.72%). Methanol extracts with a concentration of 50 mg/kg body weight produced 81.81% inhibition, which was also high as compared to the standard drug. 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 used as an anti-arthritic (Ratheesh *et al.,* 2009). *R. graveolens* extract examined in mice orally administer of the extract (200 mg/kg) show an *antinociceptive* effect (Asgarpanah and Khoshkam, 2012).

3.4. Anticancer Effects

The leaf of *Ruta* is said to alleviate cancer of the mouth, as well as tumors and warts (Chauhan and Singh, 2011). *Phenolics*, *tannins* and *flavonoids* represent major groups of *Ruta* species constituents that work predominantly as powerful antioxidants property which can control the lung, bladder, and stomach colon cancer (Ferguson *et al.,* 2004).

Patients with locally advanced solid tumors or metastases and previously treated with conventional anticancer drugs showed a transitory improvement in quality of life when given homeopathic preparation of *R. graveolens* 9C by oral administration; however, there was influence on the tumor progression (Freyer *et al.,*2014). The ultra-diluted potencies of *R. graveolens* showed anticancer activity when avoided the proliferation and cytotoxic effects on normal kidney epithelial cell model (Arora *et al.,* 2014). Total extract (70% ethanol) of *Ruta* species showed in vitro *cytotoxicity* against tumor cell lines (Varamini *et al.,* 2009).

3.5. Immuno-modulatory Effect

Ruta species was shown to stimulate immune effector cell including thymus and natural killer cell number and activity *Ethanolic* and *methanolic* extracts of *R. graveolens* leaves when administered orally, considerably increased adhesion of neutrophils to nylon fibers which interrelate to the procedure of margination of cells in blood vessels (Kumar *et al.,* 2005). *R. graveolens* extracts is concentration effective on the proliferation of interleukin (IL)-2 and interferon (INF)-y genes expression stimulation of neutrophil towards the site of inflammation (Mishra and Ratnavali, 2005). *Ruta* species extracts reduce macrophage infection through induction of nitric oxide. (Roitt *et al.,* 2002).

The humoral immunity involves the interaction of B cell with antigens and in the end proliferating and differentiating into antibody generating cells. *Alcoholic* extracts of *Ruta graveolens* leaves may be enhanced the level of IgM, IgG, and are capable of influencing B-cells, which in turn synthesize or secrete antibodies (Gokhale *et al.,* 2003).

3.6. Antibacterial Effect

More than 15 compounds in *Ruta* have been identified as having in vitro antibacterial activity; *acridone alkaloids* are the most potent antimicrobial compounds; the *coumarins* inhibit growth (Tavares and Zanon, 2014). Broad spectrum antimicrobial activity of *Alkaloids* compound is against gram positive and gram negative microorganisms such as; *Bacillus subtilis, Bacillus cereus, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes, Enterobacter aerogenes, Enterococcus species Klebsiella pneumonia, Morganella morganii* and *Enterobacter cloacae, Shigel sonnei, Salmonella typhimurium, Burkholderia cepacia, Escherichia coli,* and *Pseudomonas aeruginosa* (Ivanova *et al.,* 2005). *Ruta* species are used for gastrointestinal complaints, blackleg and nervous sensory of locomotory ailments and antisepeticin. In Mediterranean traditional medicine, Ruta has been used to treat pulmonary conditions, such as tuberculosis, and to reduce swelling of the spleen, as well as externally to treat wounds (Pollio *et al.,* 2008).

3.7. Antifungal Property

Ruta species are active ingredients have antifungal and insecticidal properties that could prove beneficial to agriculture as well (Ojala *et al.,* 2000, and Mancebo *et al.,* 2001). *Ruta* graveolens was found to have activity against various fungi such *as Aspergillusniger, A. flavus, Penicillum crysogenum, Sacharomyces cerevisae Rhizopusstolonifer, Candida albicans, Saprolegnia spp,* and *Cryptococcus* species (Oliva et al., 2003).

The presence of antifungal agent in *R. graveolens* against agriculturally important fungi in *ethylacetate* extracet similarly has demonstrated the fungicidal activity against *Colletotichum fragariae, C. gloeosporioides, C. acutatum, Botrytis cineara* and *Fusarium oxysporium*. They found that Rutacridone epoxide was the bioactive constituent from the ethylacetate extract of *R. graveolens* roots which showed fungicidal activity, *Rutacridone* epoxide also showed significantly higher fungicidal activity than commercial fungicides, *captan* and *benomyl* (Hashemi *et al.,* 2011). In *Ruta graveolens*, the existence of *saponin, tannin, alkaloid phenols, flavonoids, terpenes, and coumarins* and *glycosid* has been proved antifangal effects. *Saponin* has soap characteristics and its anti- fungal effect (Aderotimi and Samuel, 2006).

R. chalepensis are common economic food spices in Ethiopia and thus, it is an advantage to develop safe botanical food preservative against toxigenic *Aspergillus* species that have strong affinity to colonize various food commodities due to its secretion of hydrolytic enzymes and *Cladosporium herbarum* (Haddouchi *et al.,* 2013). *Dictamnine* and *furoquinoline alkaloidhas* been found to possess antifungal properties (Zhao *et al.,* 2005). Chloroform extracts isolated from the leaves of this species were active against the *Fusarium solani, Sclerotium rolfsii and Rhizoctonia solani* (Emam *et al.,* 2010).

3.8. Antiparasite Effects

The antiparasitic activity of ether extract of leaves is active against *Strongyloides stercoralis*, *nematode* that causes *strongyloidiasis*. The *molluscicidal* activity of *hexane* and *ethanol* extracts from leaves and stem of *R. graveolens* and found to be effective against the intermediate host of *Schistosoma* species (Hmamouchi *et al.,* 2000).

In vitro study performed with hydro alcoholic extract of aerial parts of *R. graveolens* show the reductions in viability, potential for invasion, and multiplication rate of the parasites *Leishmania amazonensis* and *Trypanosoma cruzi* and indicated that these *Ruta* species extract may be potential candidates for developing drugs to treat *leishmaniasis* and *Chagas* disease (Queiroz *et al.,* 2014). *Quinolinone alkaloids* is against a form of Plasmodium falciparum (Biavatti and Vieira, 2002).

In Italian countryside, *R. graveolens* leaves were set under the bed to repel bugs and mice and a decoction of *Ruta* species also has been used topically against scabies, lice, and fleas, to repel insects and to treat intestinal worms in livestock. *Rue* can also drive away pests like mosquitoes, cockroaches and flies It can also be used as *vaporizers*, *fumigants*, incense sticks and burners in-order to ward off insects (De feo *et al.,* 2002).

4. Adverse Effects Of Ruta

The standard of homeopathic therapy is which animals are diagnosed on basis of individual pattern of

clinical signs. The advocated most parenteral does is 10ml for large animal. The corresponding oral preparation of 1:1000 in tablets, globuli, or drop. Apart from the valuable medicinal properties *Ruta* species may also act toxically when overdosed, (Sharma *et al.,* 2001).

The experimental oral administration of *R. graveolens* leaves (5 g/kg) to the goats caused toxicity with pathological changes in numerous organs. The adjustments covered alterations in serum aspartate and *copper, iron, zinc, manganese, calcium,* and *phosphorus* with animal dying report. Lyophilized *hydroalcoholic* extract of aerial parts of *R. graveolens* resulted in fetal death when administered orally (1000 mg/kg/day) for the duration of the pregnancy and that Ruta species contains an alkaloid referred to as pilocarpine, that is utilized in veterinary medicinal drug to result in abortion in horses (Freitas *et al.,* 2005).

Intra-peritoneal administration high level of *R. graveolens* extracts (30 and 100 mg) in Wistar rats for three days ended in morphological modifications in the liver and caused hepatotoxicity. Aqueous extract (20%) of *R. graveolens* leaves when administered orally in rats precipitated a significant decrease inside the number of normal embryos and increase in cases of chronic late embryonic improvement accordingly demonstrating toxic impact of the extract (Benavides *et al.,*2014).

It has been reported also *ethanolic* and *aqueous* extracts of *R.graveolens* seeds resulted in change in body weight, biochemical and hematology parameters and accordingly induced *toxicity* whilst administered orally to male Wistar rats at 200 mg/kg/day (for four weeks), The *ethno* botanical look at done in health care service of pronounced the potential dangers and poisoning outcomes of *R. graveolens* such as a result of death due to stomach injury, inhibition of *spermatogenesis*, reduced concentration of *sialic acid* in the testes, epididymis and seminal vesicles together with decrease leyding cell function reflects ant-androgenic effects of *Ruta* species, anemia, weight loss and failure to grow due to lysis of red blood cell in rats (Marinoff *et al.,* 2009).

Among the impacts in human beings mention the case of 26 years old pregnant girl led to abortion after drinking *R. graveolens* tea in combination with chocolate and cinnamon. In other case; the use of decoction of *R. graveolens* through 78 years old woman caused bradycardia, renal failure with acute hyperkalemia, and coagulopathy. Additional report was indicated the case of acute phytophoto dermatitis in 2 years old child after contact with this plant species (Furniss and Adams, 2007). Nausea and vomiting are major adverse effects and care should be taken in consuming high quantities (Liao, and Yin, 2000).

5. Conclusion And Recommendation

Ruta has been used over thousands of years for medicinal purpose, and health claims credited to the ingestion of *Ruta* have predominantly come from anecdotal evidence and traditional use, it is a nature's boon to mankind. *Ruta* has health benefits such as: treatment of cardiovascular diseases, including hypertension, thrombosis and hyperlipidemias, as well as uses treatments of cancer, Alzheimer's, and diabetes. *Ruta* has also antimicrobial effect, antiparasite, antifungal, and anti-inflammatory activities. A recent increase in the popularity of alternative medicine and natural products has renewed interest in *Ruta* and their derivatives as potential natural remedies. Today with the ever-growing resistance organism, taking of *Ruta* extract remains a powerful antimicrobial agent. Although *Ruta* is believed to be a safe substance; excessive *Ruta* ingestion produces toxic effects especially on pregnant women and animals. Moreover, higher concentrations of *Ruta* powder (extract) cause considerable cell injury, anemia, weight loss, and failed to grow due to *lysis* of red blood cells.

Based on the above conclusion, the following recommendations are forwarded:

- Overdose supplementation of *Ruta* should be avoided.
- Medicinal plants like *Ruta* should be consumed as flavoring food to get constant source of medicaments for the exposure of many diseases.
- Avoid the use of Ruta during pregnancy for both human and animals.
- Future studies should be conducted on active ingredients of *Ruta* safety, efficacy, and mechanism of action, dose standardization and toxicity effects of *Ruta*.

Acknowledgments

I would like to express my special admiration and thanks to my advisors Dr. Abraha Tesfaye, for his intellectual advice, constructive suggestions and devotion of their golden time in guiding me and correcting my paper.

My deepest gratitude also extends to Mekelle University, College of Veterinary Medicine community, for their overall supports for my research activities.

Finally, I would like to acknowledge for all my colleagues for their overall support and mutual understandings during our stay in the University.

Corresponding Author:
Dr. Abraham Jemberu
Mekelle University, College of Veterinary Medicine, Ethiopia.

P.O. Box. 2084
Telephone: +251913215674
E-mail: abrishvet@gmail.com

Reference

1. Aderotimi, B. and Samuel, A. (2006). Phytochemical Screening and Antimicrobial Assessment of Abwilon Mauritianum, Bacopa Monifera and Dutera Stramonium. Biochemisry, 18(1):39-44.
2. Ahmed, OM., Moneim, AA., Yazid, IA. and Mahmoud, AM. (2010). Antihyperglycemic. Antihyperlipidemic and Antioxidant Effects and the Probable Mechanisms of Action of *Ruta Graveolens Infusion* and *Rutin* in *Nicotinamide-Streptozocin* Induced Diabetic Rats, 39(1):15-35.
3. Arora, S., Tandon, C. and Tandon, S. (2014). Evaluation of the Cytotoxic Effects of Therapies: In Vitro Study in Normal Kidney Cell Lines. *The Science World Journal,* 34:145-155.
4. Asgarpanah, J. and Khoshkam, R. (2012). Photochemistry and Pharmacological Properties of *Ruta Graveolens* L. *Journal of Medicine Plants Research,* 6(23):3942-3949.
5. Benavides, V., Trujillo, G., Arrigo, G., Paredes, U., and Pino J. (2014). Preliminar Toxicological Assessment of *Ruta Graveolens*, Origanum Vulgare and Persea Americana on the Preimplantation Mouse Embryos. Review Peru Biology, 7:87–89.
6. Biavatti, M.W. and Vieira, P.C. (2002). Biological Activity of *Quinoline Alkaloids* from *Raulinoa Echinata* and X-Ray Structure of Flindersiamine, *Journal of Brazil Chemical Society,* 13 (1):66-70.
7. Boudoir, T., Labed I., Safaei-Ghomi J., Kabouche A. and Kabouche Z. (2011). *Journal of Essential Oil Bearing Plants,* 14(6):79.
8. Chauhan, H.S., and Singh, S.K., (2011). Phytochemical Analysis, *Antioxidant* and *Anti-Inflammatory* Activities of *Phyllanthus Simplex*. *Journal of Ethno pharmacology,* 137:1337-1344.
9. Chevallier, A. (1996). The Encyclopedia of Medicinal Plants. New York, NY: DK Publishing. Pp.262-263.
10. Chien-Chih, C., Yu-Lin H., Fei-In H., Chun-Wen, W. and Jun-Chih, O. (2001). Water Soluble *Glycosides* from *Ruta Graveolens*. *Journal of Natural Production,* 64:990–992.
11. De Feo, V., De Simone F. and De Senatore F. (2002). Potential Allelochemicals from the Essential Oil of Ruta Graveolens. Phytochemistry, 61(5):573–578.
12. Emam, A., Eweis, M. and Elbadry, M. (2010). A New Furoquinoline Alkaloid with Anti-Fungal Activity from the Leaves of *Ruta Chalepensis L.* Drug Discoveries and Therapeutics, 4(6):399-404.
13. Eun-Tae, O., Ji-Ho, L., Chang-Soo, K. and Young-Soo, K. (2014). *Alkylquinolone Alkaloid* Profiles in *Ruta Graveolens*. *Journal of Biochemical System Ecology,* 57:384-387.
14. Ferguson, L., Philpott, M. and Karunasinghe, S. (2004). Dietary Cancer and Prevention using Antimutagens. *Journal of Toxicology,* 198(1-3):147-159.
15. Ferhat, M., Kabouche, A. and Kabouche, Z. (2014). Comparative Compositions of *Essential Oils* of Three Ruta Species Growing in Different Soils. *Journal of Material and Environment Science,* 5:735-738.
16. Freitas, TG., Augusto, PM. and Montanari, TH. (2005). Effect of Ruta Graveolens L. on Pregnant Mice. Contraception, 71:74–77.
17. Freyer, G., You, B., Villet, S., Tartas, S., Fournel, C., Trillet, V., Hamizi, S., Colomban, O., Chavernozn. And Falandry, C. (2014). Open Labeln controlled pilot study to evaluate Complementary Therapy with *Ruta Graveolens 9C* in Patients with Advanced *Cancer*. *Homeopathy*, 103:232–238.
18. Fullas, F. (2003). Spice Plants in Ethiopia: Their Culinary and Medicinal Applications, Reference Publications, City (USA). Pp.133–137.
19. Furniss, D., and Adams, T. (2007). Herb of Grace: An Unusual Cause of Phytophoto dermatitis Mimicking Burn Injury. *Journal of Burn Care Research,* 28:767-769.
20. Gokhale, AB., Damre, AS. and Saraf, MN. (2003). Investigations into the Immuno modulatory Activity of Argyreia Speciosa. *Journal of Ethno pharmacology*, 84:109-14.
21. Groppo., Kallunki, Pirani. and Antonelli. (2012). Chilean Pitavia More Closely Related to Oceania and Old World *Rutaceae* than to *Neotropical* Groups: Evidence from Two *DNA* Non-Coding Regions, with a new Sub Familial Classification of the Family. Phytokeys, 19:9-29.
22. Haddouchi, F., Chaouche, T., Zaouali, Y., Ksouri, R., Attou, A. and Benmansour, A. (2013). Chemical Composition and *Antimicrobial* Activity of the *Essential Oils* from Four *Ruta* Species Growing in Algeria. Food Chemical, 141:253-258.
23. Hammiche, V., Merad, R. and Azzouz, M. (2013). In Plantes Toxiques À Usage Medicinal Du Pour Tour Mediterranean. Springer Paris. Pp.197-222.
24. Hashemi, K., Sadeghpour, H., Gholampour, A. and Mizaei J. (2011. Survey The *Antifungal* Effecte of Root Ethanolic Extract of *Ruta Gravenolens* on Saprolegnia. International

Conference on Biothechnology and Environmental Management, 18:19-23.
25. Hmamouchi, M., Lahlou, N. And Agoumi, A. (2000). Fitoterapia,71(3):308-314.
26. Hussain, SA., Numan, IT. and Hamad, MN. (2012). Comparative Study of the Analgesic activity of Two Iraqi Medicinal Plants, *Ruta Graveolens* and *Matricaria Chamomilla Extracts*. *Journal of Intercult Ethnopharmacology,* 1:79- 83.
27. Hyun, TK. And Kim, JS. (2009). The Pharmacology and Clinical Properties of *Kalopanax* Pictus. *Journal. Medicinal. Plants Research,* 3(9):613-620.
28. Iauk, K., Mangano, A., Rapisarda, S., Ragusa, L., Maiolino, R., Musumeci, R., Costanzo, and Serra A. (2004). *Journal of Ethno pharmacology,* 90:267-272.
29. Ivanova, A., Microvax, B., Najdenski, H., Tsvetkova, I. and Kostova, I. (2005). *Antimicrobial* and *Cytotoxic* Activity of *Ruta Graveolens*. Fitoterapia,76(3- 4):344-347.
30. Kostova, I., Ivanova, A., Mikhova, B. and Klaiber, I. (1999). *Alkaloids* and *Coumarins* from *Ruta Graveolens*. Monatsh Chemical, 130:703–707.
31. Kumar, SR., Narayanaperumal, JP. and Rathisamy, SD. (2005). Immuno-Modulatory Activity of Triphala Over Neutrophil Functions. Biology *Pharmacology* Bull, 28:1398-403.
32. Kuzovkina, I., Al'termana, I. and Schneiderb, B (2004). Specific Accumulation and Revised Structures of *Acridone Alkaloid Glucosides* in the Tips of Transformed Roots of *Ruta Graveolens*. *Phytochemistry*, 65:1095–1100.
33. Liao, K. And Yin, M. (2000). Individual and Combined Antioxidant Effects of Seven *Phenolic* Agents in Human Erythrocyte Membrane Ghosts and Phosphatidylcholine Liposome Systems: Importance of the Partition Coefficient. *Journal of Agriculture and Food Chemistry,* 48:2266-2270.
34. Linder N, Martelin E, Lapatto R, Raivio K. (2003). Post-Translational Inactivation of Human Xanthine Oxidoreductase by Oxygen under Standard Cell Culture Conditions. American. *Journal of Cell Physiology*, 285: 48-5.
35. Mancebo, F., Hilje, L., Mora, G., Castro, V. and Salazar, R. (2001). Biological Activity of *Ruta Chalepensis* (*Rutaceae*) and *Sechium Pittieri* (*Cucurbitaceae*) *Extracts* on Hypsipyla *Grandella* (*Lepidoptera: Pyralidae*) *Larvae*. Review Biology Trop, 49:501-508.
36. Marinoff, MA., Martinez, JL. And Urbina. MA. (2009). Precauciones Elempleode Plantas *Medicinales*. Latinoam Caribe, 8:184–187.
37. Meepagala, KM., Schrader, KK., Wedge, DE. and Duke, SO. (2005). *Algicidal* and *Antifungal* Compounds from the Roots of *Ruta Graveolens* and Synthesis of their Analogs. Phytochemistry, 66:2689–2695.
38. Milesi, S., Massot, B., Gontier, E., Bourgaud, F. And Guckert, A. (2001). *Ruta Graveolens*. Apromising Species for the Production of *Furanocoumarins*. Plant Science, 61:189–199.
39. Mishra, S. and Ratnavali, B. (2005). (1sted.). Varanasi Chaukambha Surbhatri Prakashan, Pp. 108-133.
40. Ojala, T., Remes, S., Haansuu, P., Vuorela, H., Hiltunen, R., Haahtela, K. and Vuorela. P. (2000). *Antimicrobial* Activity of Some *Coumarin* Containing Herbal Plants Growing in Finland. *Journal Ethno pharmacology,* 73:299-305.
41. Oliva, A., Lahoz, E., Contillo, R. and Aliotta, G. (1999). *Fungistatic* Activity of *Ruta Graveolens* Extract and its *Allelochemicals*. *Journal Chemistry of Ecology*, 25:519–526.
42. Oliva, AG., Meepagala, KM., Wedge, DE., Harries, DE., Hale, AL., Aliotta, GP. and Duke, SO. (2003). Natural Fungicides from *Ruta Graveolens L.* Leaves, Including a New *Quinolone Alkaloid*. *Journal Agriculture Food Chemistry*, 51:890–896.
43. Pérez-Vizcaino, F., Duarte, J., Jiménez, R., Santos-Buelga, C. and Osuna, A. (2009). Antihypertensive Effects of the *Flavonoid Quercetin*. Pharmacology Report, 61:67-75.
44. Pollio, A., Natale, A., Appetiti, E., Aliotta, G. and Touwaide, A. (2008). Continuity and Change in the Mediterranean Medical Tradition: *Ruta* Species. (Rutaceae) in Hippocratic Medicine and Present Practices. *Journal Ethno Pharmacology*, 116(3):469-482.
45. Prabhu, S., Vijayakumar, S., Morvinyabesh, J., Ravichandran, K. and Sakthivel, B. (2014). Documentation and Quantitative Analysis of the Local Knowledge on Medicinal Plants in Kalrayan Hills of Villupuram District, Tamil Nadu, India. *Journal Ethno pharmacology*, 157:7–20.
46. Proestos, C., Boziaris, I., Nychas, G. and Komaitis, M. (2006). Analysis of *flavonoids* and *Phenolic Acids* in Greek Aromatic Plants: Investigation of Their Antioxidant Capacity and Antimicrobial Activity. Food Chemistry, 95:664–671.
47. Queiroz, A., Freire, T., Matta, C., Silva, L., Araujo, J., Araujo, G., Moura, F. and Alexandre, M. (2014). Antileishmanial Activity of Medicinal Plants used in Endemic Areas in Northeastern

Brazil. *Journal of Evidences Based Complement and Alternative Medicine.* Pp.1-9.
48. Raghav, S., Gupta, B., Agrawal, C., Goswami, K. and Das, H. (2006). Anti Inflammatory Effect of Ruta Graveolens L. in Murine Macrophage Cells. *Journal Ethno pharmacology,* 104:234-239.
49. Ratheesh, M. and Helen, A. (2007). Anti-Inflammatory Activity of Ruta Graveolens Linn On Carrageenan Induced Paw Edema in Wistar Male Rats. *Africa Journal of Biotechnology,* 6(10):1209-1211.
50. Ratheesh, M., Shyni, G., Sindhu, G. and Helen, A. (2009). Inhibitory Effect of *Ruta Graveolens* L. on Oxidative Damage, Inflammation and Aortic Pathology in *Hypercholesteromic* Rats. Experiment Toxicology and Pathology, 63(3):285- 290.
51. Raz, I., Eldor, R., Cernea, S. and Shafrir, E. (2005). Diabetes, Insulin Resistance and Derangements in Lipid Metabolism Cure through Intervention in Fat Transport and Storage. Diabetes Metabolism Research, 21: 3-14.
52. Roitt, I., Brostoff, J. and Male, D. (2002). In: Immunology. (3rdEd.) Mosby-Year Book Ltd., London. Pp.7.
53. Saieed, P., Reza, R., Abbas, D., Seyyedvali, R. and Aliasghar, H. (2006). Inhibitory Effects of *Ruta Graveolens L. Extract on* Guinea Pig Liver *Aldehyde Oxidase. Chemistry Pharmacology*, 54:9–13.
54. Salib, JY., El-Toumy, SA., Hassan, EM., Shafik, NH., Abdel-Latif, SM. and Brouard, IE. (2014). New *Quinolines Alkaloid* from *Ruta Graveolens Aerial* Parts and Evaluation of the Antifertility Activity. Natural Product Lett: Formerly, 28:1335–1345.
55. Schmidt, R., Stocker, C. and Vollbracht, M. (2015). Antioxidants in Translational Medicine *Antioxidants* and Redox Signaling, 23(14):1130-1143.
56. Scott, K., Mcintyre, C. and Playford, J. (2000). Molecular Analyses Suggest a Need for a Significant Rearrangement of *Rutaceae* Subfamilies and a Minor Reassessment of Species Relationships Plant Systematics and Evolution, 223:1525-1527.
57. Shanazi, S., Yezdani. D., Ejni, Y. (2006). Study on the Business of Medical Plants in The World and Iran. Seminar of Medical Plants. Azad University, Sharekord, Iran. Pp.313.
58. Sharma, AN., Nelson, LS. and Hoffman, RS. (2001). *Ruta Graveolens* as an Ethnic Abortifacient. *Journal of Toxicological* and Clinical Toxicology, 39:306-312.
59. Soleimani, M., Aberoomand-Azar, P., Saber-Tehrani, M. and Rustaiyan, A. (2009). Volatile Composition of *Ruta Graveolens L.* of North of Iran. World Application. *Science Journal,* 7:124–126.
60. Tavares, L. and Zanon, G. (2014). Structure Activity Relationship of Benzophenanthridine Alkaloids from Zanthoxylum Rhoifolium Having Antimicrobial Activity. Plos One, 9(5).
61. Varamini, P., Soltani, M. and Ghaderi A. (2009). Cell Cycle Analysis and *Cytotoxic* Potential of *Ruta Graveolens* against Human *Tumor Cell* Lines. Neoplasma, 56:49-58.
62. Verma, S. K., and Kumar, A.G. (2011). Therapeutic Uses of Withania Somnifera (Ashwagandha) With a Note on with Anolides and its Pharmacological Actions. *Asian Journal of Pharmaceutical and Clinical Research,* 4:1-4.
63. Wallace, L., Boilard, S., Eagle, S., Spall, J., Shokralla, S. and Hajibabaei M. (2012). DNA Barcodes for Everyday Life: Routine Authentication of Natural Health Products. *Food Research International,* 42:446-520.
64. Zhao, Y., Chen, Y., Chang, F. and Tzeng, C. (2005). Synthesis and Cytotoxic Evaluation of Certain 4-Anilino-2-Phenylquinoline Derivatives, *European Journal of Medicinal Chemistry,*40:792-797.
65. Zobel, A. and Brown, S. (1990). Dermatitis-Inducing Furanocoumarins on the Leaf Surfaces of Eight Species of Rutaceous and Umbelliferous Plants. *Journal of Chemical Ecology*. 16(3):693-700.