Medical Journal of Ahl al-Bayt University, Vol.3, No.1, Aug.2024

Potential of some therapeutic effect of ruta graveolenes plant and their bioactivities: A review

Hinda Ali[1], Atheeb Ahmed K. [2], Abeer Qais Abdulwahab[3]

[1]**hinda1993@uomustansiriyah.edu.iq**

[2]**ahmed.k.odhaib@uotechnology.edu.iq**

[3]**abeerqaya2000@uomustansiriyah.edu.iq**

[1,3] Department of pharmaceutical chemistry, College of pharmacy, University of mustansiriyah, Iraq

[2] College of chemical engineering, University of technology, Iraq

ABSTRACT

Herbal medicine, often known as herbalism or phytotherapy, is an alternative healthcare strategy that uses plants and their extracts to treat various pathological problems. Flavonoids are the main group of plant secondary metabolites and are present in the tissues and organs of various plant species. Flavonoids are essential for various biological processes and can be influenced by a diverse array of environmental factors in plants. The rutaceae is an extensive botanical family comprising a multitude of genera and species. The rutaceae family consists of a large variety of aromatics plants, predominantly located in tropical areas. The rutaceae family of plants is extensively employed in traditional medicine in various places worldwide. A highly common plant from this botanical family is Ruta graveolens L., commonly known as "Rue," "Sudab,". Ruta graveolens plays a wide variety of important roles in plants. It has antioxidant, anti-inflammatory, antidiabetic, antibacterial, cardioprotective, and anticarcinogenic properties. This article offers a succinct summary of the most recent breakthroughs in ruta graveolenes research, with the goal of aiding in the recognition of their medicinal characteristics.

Key words: Herbal medicine, Flavonoids, Ruta gravolenes, Sudab, Antioxidant

1.Introduction:

1.1. Herbs (Medical plants)

Herbal medicine, commonly referred to as herbalism or phytotherapy, is an alternative approach to healthcare that utilizes plants and their extracts to treat different pathological disorders. Various components of herbs, such as flowers, leaves, roots, or other plant parts, can be utilized in pharmaceutical formulations to provide specific therapeutic advantages [1]. Medicinal plants have a crucial function in healthcare and have been predominantly used by Asians and

Africans for a significant period of time, relying on acquired experiential knowledge [2]. According to reports, approximately 70 to 80 percent of Africa's growing urban and rural population rely on herbal medicine to treat health concerns [3]. Furthermore, billions of individuals worldwide are regularly consuming herbal medicine in the form of pharmaceutical medications or dietary supplements [4]. Several studies have documented the efficacy of medicinal herbs in the prevention and treatment of various diseases, including gastrointestinal ailments, malignancies, viral infections, stress, and anxiety [5-8]. Medical herbals have been utilized to enhance mental well-being within the Covid-19 pandemic [9,10]. Herbal medications prioritize the combined effect of multiple components rather than relying on a single molecule. Assessing the specific contributions of individual constituents in medicinal herbs to their therapeutic effects, as well as understanding how these chemicals function together in synergy, is a challenging task [11]. The pharmacodynamic material foundation of herbal medicines refers to the active chemical components that are responsible for the clinical efficacy of the drugs [12]. In contrast to modern medical approaches, the utilization of herbal medicines primarily relies on the application of practices and notions derived from ancient philosophy. The integration of evidence-based medicine and modern medical practice procedures is crucial for the advancement of herbal medications [13]. However, the intricate nature of the interactions between herbal medicines and the human body has resulted in limited evidence regarding the pharmacodynamics, pharmacokinetics, safety, and efficacy of these medicines. Currently, medical herbs have become a primary focus for both health authorities and the general population [14].

Hence, it is crucial to have sustainable management practices for traditional herbal medicine, as well as to address the reactions and challenges involved in monitoring and ensuring the safety of plant resources. These practices serve as valuable sources for the development of new drugs that can be used to treat a wide range of diseases, from common body pain to more complex conditions in humans [15-16].

1.2. Ruta Graveolens

The Rutaceae is an extensive plant family with numerous genera and species. It is primarily widespread in tropical and subtropical climates globally [17]. This plant is grown on infertile rocky terrain and is indigenous to both North Africa and South Europe [18-20].

The Rutaceae family is employed in traditional medicine in several locations across the globe. A highly common member of this family is Ruta graveolens L., also known as "Rue" or "Sudab" or "Sadab". A plant is an ornamental perennial shrub that may grow up to a height of 1 meter and has notable medicinal properties. More than one hundred twenty natural compounds have been found in different parts of this plant. These chemicals are mostly composed of coumarines, acridone alkaloids, essential oils, fluroquinolines, and flavonoids [21]. Furthermore, it functions as the main storage site for furanocoumarins, including psoralen, xanthotoxin, and bergapten [22]. The extracts of R. graveolens L, obtained from different sections of the plant such as the leaves, have been used for diverse purposes. Rue has been traditionally employed in medicine as a stimulant for the menstrual cycle, a sedative, and an antispasmodic [23]. Rue extracts

were used as abortive agents in some cultures [24]. Nevertheless, it is crucial to acknowledge that rue is not frequently employed for the treatment of diverse pulmonary disorders, the reduction of swelling, or the healing of wounds [25]. Plants contain coumarin compounds in their essential oils, which enhance their medicinal effects. The derivatives mentioned are furocoumarines, specifically psoralene, xanthotoxin, bergapten, isopimpinelin, xanthoxanthine and rutamarin as well as quinoline type alkaloids [26]. Ruta graveolens L. (Rutaceae) has been found to possess notable therapeutic qualities in memory problems and in increasing learning [27], with minimal occurrence of adverse effects [28]. Rutin, a flavonoid, has attracted the interest of researchers [29]. Rutin, a prominent constituent of R. graveolens, enhances memory retrieval and exhibits several pharmacological properties including anti-allergic, anti-inflammatory, anticancer, antiviral, and antimycotic attributes [30].

1.3. Flavonoids

Flavonoids are an essential group of organic compounds that belong to the family of plant secondary metabolites. They have a polyphenolic structure and are commonly found in vegetables, fruits, and specific beverages. Flavonoids are found in the early stages of plant development. Pigments such as chlorophylls and carotenoids are plentiful and contribute to the scent and flavor of fruits, flowers, and seeds. Flavonoids have biochemical and antioxidant actions that are linked to a range of disorders, including cancer, Alzheimer's disease (AD), and atherosclerosis [31-33]. Flavonoids are polyphenolic secondary metabolites that are commonly present in plant fruits and vegetables, as depicted in figure (1), as well as in fungi. Flavonoids consist of two phenolic rings, a heterocyclic ring containing an oxygen atom, and a total of fifteen carbon atoms [34]. According to ethnobotanical research, around eight hundred plants are believed to possess anti-diabetic properties [35-37].

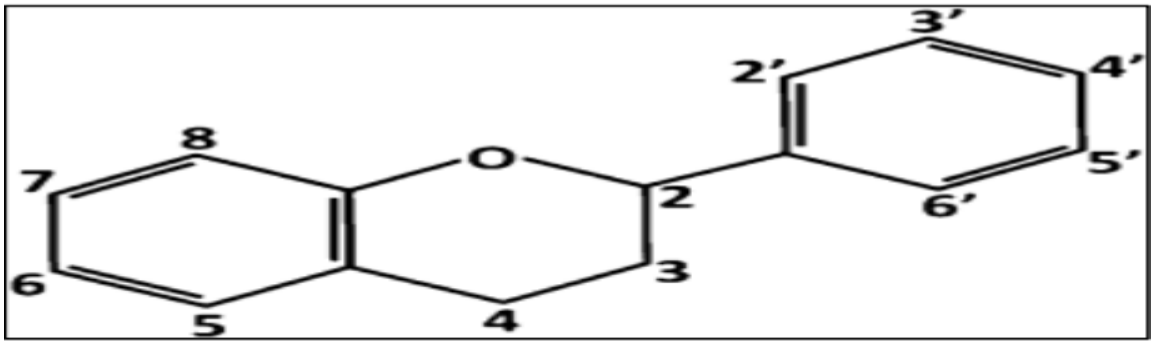

Figure (1): structure of Flavonoids

Flavonoids are abundant in plant sources such as fruits and vegetables. Flavonoids possess several biological actions, including organ protection, anti-inflammatory properties, lipid-lowering effects, antioxidant effects, and hypoglycemic effects. Flavonoids have a significant impact on the development of diabetes and its consequences via regulating glucose metabolism, hepatic enzyme activity, and lipid profile [38].

Quercetin and rutin are the main active flavonoids found in Ruta graveolens. Rutin, initially derived from the leaves of the plant, possesses a notable presence. In addition, the volatile oil of Ruta graveolens includes a significant number of ketones, aliphatic acids and alcohols. Ruta graveolens is distinguished by its significant synthesis of linear furanocoumarins, particularly psoralen and methoxypsoralen [39]. Rutacridone, rutacridone epoxide, and gravacridondiol, which are acridone alkaloids, have been isolated from the plant's root [40]. Moreover, researchers have effectively isolated an alkaloid called graveoline from the plant's leaves [41].

2. Therapeutic Properties of Ruta graveolens

Ruta graveolens perform a diverse range of significant functions in plants. It possesses antioxidant, anti-inflammatory, antidiabetic, antibacterial, cardioprotective, and anticarcinogenic effects.

2.1. Antioxidant

For a long time, natural goods have been acknowledged as a useful reservoir of bioactive compounds for the advancement of pharmaceutical medications. The majority of the medications that have already been created were obtained from plant specially that were previously employed as traditional herbal remedies [42]. Scientists are growing more interested in obtaining natural antioxidants from plant materials as a substitute for artificial antioxidants. Antioxidants are molecules that possess the ability to shield against the harmful effects of free radicals. The antioxidants can function at several stages (prevention, interception, and repair) by providing hydrogen, decreasing singlet oxygen, acting as chelators, and capturing free radicals through different mechanisms. The number 43 is enclosed in square brackets. (ROS) Reactive oxygen species and (RNS) reactive nitrogen species have the ability to harm biological components such as proteins, lipids, DNA and carbohydrates, and leading to the development of different pathological diseases [42].

The actions of free radicals are regulated by a system of internal enzymatic and non-enzymatic antioxidants that remove pro-oxidants and capture free radicals [43]. The primary reason for the antioxidant activity of plant extracts is the presence of phenolic compounds, including flavonoids, phenolic acids, and phenolic diterpenes. Naturally occurring antioxidant agents have garnered significant attention due to their ability to safeguard the human body against free radicals. The genus Ruta is comprised of three extensively distributed and extensively researched species: Ruta montana L., Ruta chalepensis L. and Ruta graveolens L. [44].

R. graveolens is known to possess a wide range of actions, such as antibacterial, antioxidant, pasmolytic, sedative and anti-inflammatory characteristics. Ruta graveolens contains phenolic chemicals that act as potent antioxidants, effectively counteracting free radicals by giving an electron or hydrogen atom. Rutin, which is the primary component of R. graveolens, is widely known for its ability to enhance memory recall and has pharmacological properties including anti-inflammatory, antiviral, and antioxidant actions. The number 48 is enclosed in square brackets. Oxidative metabolism is crucial for the survival of cells, but also leads to the creation of free

radicals and other reactive oxygen species [42]. Elevating the concentration of free radicals in the body leads to the occurrence of oxidative stress, a condition that contributes to the development of degenerative and chronic diseases such as rheumatoid arthritis, autoimmune disorders, cataract, aging, cancer, neurological diseases and cardiovascular diseases [43].

2.2. anti-inflammatory

Inflammation is an intricate biological reaction to pathogens and tissue damage, which involves a variety of inflammatory mediators and immune cells. Non-steroidal anti-inflammatory medications (NSAIDs) are commonly used to reduce inflammation and alleviate pain by blocking the formation of prostaglandins through the inhibition of COX-1 and COX-2 enzymes. Ruta graveolens, belonging to the Rutaceae family, has a long-standing historical application in Ayurveda, Homeopathy, and Unani medicine. The material comprises a diverse array of chemical components, including as flavonoids, acridone alkaloids, essential oils, coumarins, and fluoroquinolones. These compounds are accountable for its capacity to diminish inflammation and relieve discomfort (45). The comparative analysis of Ruta graveolens and allopathic medications, such as NSAIDs, demonstrates the potential of Ruta graveolens as an alternate method for managing inflammation and pain. Although NSAIDs have frequently been utilized for these goals, they are linked to significant adverse effects, such as gastrointestinal and renal problems.

Ruta graveolens, a plant with a significant historical role in traditional medicine, offers an interesting option because of its wide range of bioactive components, such as acridone alkaloids, coumarins, essential oils, flavonoids, and fluoroquinolones. The investigation indicates that Ruta graveolens may provide a less risky alternative with less severe side effects, making it an appealing choice for persons who are unable to endure the negative effects of NSAIDs.
However, it is necessary to emphasize the necessity for additional comprehensive research and clinical trials to confirm the complete safety profile and efficacy of Ruta graveolens. Furthermore, it is imperative to examine the specific dosage forms and modes of administration for Ruta graveolens to establish accurate guidelines for its usage. This study examined the anti-inflammatory properties of skimmianine (SKM), a quinoline alkaloid derived from Ruta graveolens, in a rat model of acute inflammation caused by carrageenan. Treatment with a dose of 5.0 mg/kg of SKM led to a notable reduction in paw swelling and a decrease in the levels of pro-inflammatory markers TNF-a and IL-6 mRNA. Additionally, it reduced the concentrations of inflammatory mediators such as PGE2 and NO, as well as the enzymatic activity of COX-2 and 5-LOX. The implementation of SKM therapy led to a decrease in the presence of neutrophils, lipid peroxidation, and oxidative stress in the tissue of the paw. The results suggest that SKM has potential as an anti-inflammatory drug by targeting many pathways, making it a viable therapy choice for various inflammatory disorders [41].

2.3. anti-diabetic activity

Diabetes mellitus is a long-term metabolic disorder that involves irregularities in the metabolism of carbohydrates, lipids, and lipoproteins. This condition can lead to several consequences, including hyperlipidemia, hyperinsulinemia, hypertension, and atherosclerosis. Diabetics may experience cell and tissue damage and an acceleration of diabetic consequences due to an imbalance between oxidative stress and anti-oxidative defense mechanisms. Oxidative stress can exert a substantial impact on the glucose transport protein (GLUT) or the insulin receptor. Antioxidants that combat oxidative stress may potentially lower elevated levels of glucose in the bloodstream in individuals with diabetes, hence potentially improving the condition and mitigating its associated problems. Ruta graveolens, which contains potent phytochemical components, particularly flavonoids, can be utilized as a natural medication for treating hyperglycemia. The flavonoids in it act as antioxidants, which help to safeguard the kidneys from renal failure. Examining the impact of Rue chemical components on diabetic patients, either independently or in conjunction with synthetic medications, can prove beneficial. It is recommended to include Rue aerial portion in the human diet as a prescription. The study examined the impact of total and flavonoid extracts from Ruta graveolens on blood glucose, cholesterol, triglycerides, and urea levels in rats. The results were compared to those of synthetic medications [46,]. The study found that the aerial component of Rue had beneficial effects on diabetic rats, making it a potential therapy option [47]. Additionally, a study demonstrated a reduction in blood glucose levels in diabetic rats induced by STZ through the use of an aqueous extract from the aerial parts of Rue. The antidiabetic properties of R. graveolens, in addition to three other plants, have been documented in traditional remedies for the treatment of diabetic patients. Nevertheless, a study [48, 49, 50] concluded that Rue did not possess a substantiated anti-diabetic effect. However, the study's findings demonstrated that both R. graveolens and Rutin possess qualities that can lower blood sugar levels and reduce fat levels in the blood. These effects are attained by their capacity to stimulate insulin secretion, decrease the absorption of glucose and cholesterol in the intestines, enhance the efficacy of insulin in the body, influence factors that contribute to insulin resistance, improve the uptake of glucose in peripheral tissues, and reduce the production of glucose by the liver. In this scenario, R. graveolens and Rutin have a beneficial effect on the antioxidant status.Their findings indicate that both Rue and Rutin enhance glucose tolerance by improving the structure of the islets, increasing insulin release, improving insulin binding affinity, enhancing peripheral glucose uptake, reducing intestinal glucose absorption, and decreasing the activity of gluconeogenic and glycogenolytic enzymes[50]. Flavonoids also have the ability to regulate carbohydrate digestion, insulin production, insulin signaling, glucose absorption, and adipose deposition, which contributes to their antidiabetic effect [51].

They selectively target several molecules that play a role in regulating many pathways, including enhancing the growth of β-cells, stimulating insulin production, reducing cell death, and decreasing high blood sugar levels by controlling glucose metabolism in the liver [52]. Scientific literature has documented the antioxidative, anti-inflammatory, and antihyperglycemic properties of flavonoids. These properties are crucial in reducing the likelihood and impact of diabetic complications, including retinopathy, nephropathy, neuropathy, and cardiovascular disease.

Moreover, flavonoids can enhance insulin sensitivity and glucose metabolism, which may be beneficial for glycemic management [59]. The molecular and cellular mechanisms, although not completely comprehended, encompass a broad range of metabolic pathways and are now under investigation. These findings underscore the importance of conducting robust, randomized, placebo-controlled intervention trials in individuals experiencing problems associated with diabetes. Furthermore, it is imperative to conduct randomized controlled trials using the latest anti-diabetic drugs to determine the efficacy of flavonoid activity as an adjuvant rather than a primary medical treatment. Additional research may provide further understanding on the optimal methods of utilizing these naturally existing compounds to improve the quality of life for those with diabetes and reduce the impact of diabetic complications [60].

2.4. Antibacterial activity occurs in ruta graveolenes

Bacterial and fungal pathogens are responsible for numerous human diseases, resulting in fatalities particularly in developing nations. Additionally, they have an impact on the production cycle of field crops, namely during the field growing stage and in post-harvest facilities [61]. Typically, antibiotics and commercial reagents are used to manage these germs. However, microbes have evolved into strains that are resistant to many drugs, enabling them to survive the application of antibiotics or commercial reagents [62]. These antibiotics and commercial reagents possess multiple adverse effects, thereby necessitating a quest for safer alternatives. Consequently, scientists are exploring novel resources that can regulate the growth of these bacteria and fungi, such as secondary plant compounds, including essential oils (EO). Using SWE mixes of various algae species could be an innovative method to enhance the therapeutic yield of the essential oil of R. graveolens. This study is the first to investigate the potential of combining several marine algae species to stimulate the production of the primary essential oil components in the aromatic plant R. graveolens. This application could have significant benefits for the pharmaceutical industry, as these essential oil constituents have antibacterial and anticancer properties [63].

Multiple investigations have demonstrated that plants release flavonoids as a reaction to bacterial infection. According to Cushnie and Lamb [53], it has been demonstrated that flavonoids such flavone glycosidase, galangin, apigenin, and chalone possess antibacterial characteristics. A diverse range of flowering plants and nonflowering medicinal herbs exhibit antibacterial activity through the presence of many flavonoids. Asplenium nidus nidus L. is a fern that includes gliricidin 7-O-hexoside and quercetin-7-O-rutinoside. This fern provides protection against three pathogens: Proteus mirabilis Hauser, Pseudomonas aeruginosa (Schroeter), and Proteus vulgaris [54]. According to a study conducted by Pavić V, Flačer D, and colleagues, extracts from R. graveolens shown inhibitory effects on gram-positive bacteria including Streptococcus pyogenes, Staphylococcus aureus, Bacillus subtilis and Listeria monocytogenes [68]. Additionally, previous research has demonstrated that several rue components impede the process of DNA replication, hence preventing the reproduction of certain viruses [65]. Flavonoids are utilized in the treatment of skin acne and exhibit antibacterial properties against P. acnes. The first flavonoid antibiotic against fungi is chloroflavin, which contains chlorine. Oranges include flavonoids that can help fight against Deuterophoma tracheiphila, a type of fungus.Myricetin, a flavonoid, hampers the

proliferation of Burkholderia cepacia, a type of bacteria that exhibits resistance to multiple drugs. Additionally, myricetin impedes the process of protein synthesis in B. cepacia [55].

2.5. Cardio protection.

Multiple studies have demonstrated the efficacy of flavonoids in safeguarding the heart. Flavonoids can be used to prevent hypertension and atherosclerosis. These flavonoids decrease pressure in the atria, improve the process of relaxing blood vessels, and avoid malfunction in the endothelium. Endothelial dysfunction, a prominent factor in cardiovascular disease, is the primary consequence arising from atherosclerosis and the production of arterial thrombus. Anthocyanin delphinidin induces vasorelaxation by its effect on the endothelium. The process of atherosclerosis initiation begins with the oxidative alteration of low-density lipoproteins by free radicals. Scavenger receptors facilitate the uptake of this changed LDL, resulting in the creation of cells [56]. The activity of quercetin and quercetin glycosides protects LDL against oxidative alteration, hence achieving cardio protection. Polyphenolics has antioxidant properties that can have substantial health advantages. The ability of polyphenols to chelate ferrous ions and scavenge reactive oxygen species (ROS) is responsible for their role in protecting against chronic cardiovascular activity [57].

2.6. Anti-cancer

Cancer is a significant health issue that arises from the improper proliferation of cells. There are various types of anticancer drugs, but only a small number of them effectively suppress the development of cancer without causing negative side effects. Natural macromolecules containing secondary metabolites possess Phyto mediated content and exhibit a diverse variety of biological actions, forming the foundation for the prevention and treatment of cancer. Several studies indicate that flavonoids can suppress cell proliferation and function as an anticancer drug [67]. Chemoprevention refers to the utilization of natural or manufactured agents to impede the process of carcinogenesis [68,69].

Antitumor activity was discovered in Ruta graveolens. It has a notable impact in prolonging the longevity of mice with ascites DLA and EAC tumors. Additionally, it was discovered that it decreased the size of the solid tumor in animal models. Treatment with Ruta graveolent extract greatly enhanced the survival rate of rats with solid tumors. However, it was discovered that the activity did not vary based on concentration. When the higher concentration was employed, the activity was seen to be diminished compared to the lower dosage in both the ascites and solid tumor models. This decrease in activity may be attributed to the toxicity of the Ruta graveolent extract, as previously documented [70]. Remarkably, it has been discovered that the homeopathic dilution of Ruta, specifically the Ruta 200c, is equally efficacious in treating ascites and solid tumors. According to previous findings, it has been found that the homeopathic dilution of Ruta exhibits anticlastogenic action [70]. Experiments conducted in a controlled laboratory environment to assess the antioxidant activity of Ruta graveolent demonstrated that, when used in higher concentrations, it exhibited pro-oxidant properties rather than antioxidant properties. However, when the content of Ruta graveolent extract was reduced, it was seen that it effectively

eliminated hydroxyl radicals and prevented lipid peroxidation. Pro-oxidants can alter the redox potential within cells, and it has been documented that they directly impact the mitochondrial permeability transition pore [70]. It triggers the opening of the mitochondrial permeability transition pore, resulting in apoptosis. The data indicate that the extract of R. graveolens contains prospective chemicals that should be further studied to determine their mechanisms of action, as well as their potential for use in chemotherapy or as adjuvant therapy. Significantly, the administration of the extract resulted in the development of nuclear foci, which is a distinct feature of conventional DNA-damaging agents employed in cancer treatment, such as radiation and platinum compounds. In addition, even the lower quantities that were examined still suppressed the growth of cells in the colony formation experiment, indicating the existence of persistent elements that hinder the proliferation of cancer cells at low dosages of the extract. At low doses, there was no substantial presence of abnormal cell divisions, indicating a possible distinct mode of action at low doses compared to high doses, where DNA damage and abnormal cell divisions were observed. Hence, it is justified to explore the therapeutic (high dose) or chemo preventive (low dose) capabilities of the extract and its constituents [71,72].

A study was conducted on women with hormone-receptor positive breast cancer who received treatment with aromatase inhibitors (AIs). The study examined the effects of including homeopathic medications Ruta graveolens 5CH and Rhus Toxicodendron 9CH.
seemed to enhance the relief of joint pain and stiffness over a three-month period, in comparison to those who did not use these remedies. The homeopathic group saw a lower incidence and less severe symptoms of joint pain as a side effect of AI medication. These data indicate possible advantages, but it is necessary to conduct larger research with a placebo control group in order to validate them. In France, complementary therapies such as homeopathy are frequently employed in conjunction with conventional cancer treatment to effectively address side effects and enhance the overall well-being of cancer patients. Oncologists consider these therapies to be beneficial for treating conditions such as hot flashes, musculoskeletal pain, weariness, neuropathies, dry eyes and sleep disturbances, anxiety. The text is enclosed in the tag [73]. The pilot observational study (74) found that the homeopathic remedies Ruta graveolens 5CH and Rhus Toxicodendron 9CH may alleviate joint pain and stiffness associated with aromatase inhibitors in women with early breast cancer. Ruta graveolens is employed for the treatment of adverse effects caused by radiation therapy, such as cutaneous burns and inflammation. Additionally, it may play a role in the management of symptoms connected to bones in individuals with cancer. The number 62 is enclosed in square brackets. The plant Ruta Graveolens is the origin of the anticancer chemical isopimpinellin. Multiple research have investigated the impact of isopimpinellin as an anticarcinogenic agent. It functions as a suppressor of skin tumor and breast cancer. In their investigation on mouse skin models, Mistry Prince et al. demonstrated the anti-carcinogenic properties of naturally occurring coumarins, specifically isopimpinellin. In addition, they assessed the suppression of 7, 12-dimethylbenz [a] anthracene (DMBA) and DNA adduct formation using this method. The study conducted by Heather E. Kleiner et al. assessed the impact of orally administered isopimpinellin on skin tumors induced by the application of benzo[a]pyrene (B[a]P)

and 7,12-dimethylbenz[a]anthracene (DMBA). The initial dose resulted in a notable 37% inhibition of B[a]P-DNA adduct formation. Subsequently, oral administration of three different doses (35, 70, and 150 milligrams per kilogram) led to inhibitions of DMBA-DNA complex formation by 23%, 56%, and 69%, respectively, as observed in the study. The range of numbers from 81 to 83. Under certain stress situations, these substances function as both poisons and antibiotics. They play a crucial role in plants and are also essential for human health due to their diverse pharmacological effects. Certain flavonoids are recognized as pigments found in flowers, responsible for providing color and scent [3]. Flavonoids exhibit a wide range of impacts on microbes and animals, encompassing many structures and functions. Over 9,000 derivatives of flavonoids have been reported since that time. A diverse array of derivatives is crucial for maintaining the structural integrity of plants, protecting them from harmful UV radiation, facilitating reproduction, regulating cell signaling, and influencing physiological processes. Flavonoids are bioactive phytochemicals that are widely present in plants and have been utilized in herbal treatments for a considerable period of time. They are a crucial component of our everyday food intake. They primarily accumulate in the consumable portions of plants [80]. To effectively address the treatment of a complicated chronic condition, numerous elements must be considered. In conventional treatment, this often involves the use of multiple medications, which is known as polypharmacy. Thus, it is crucial to highlight that herbal medicines are intricate mixtures of various major and minor ingredients, possessing multiple powerful targets and processes. The review demonstrated that Ruta graveolens, a medicinal herb, has bioactive chemicals that hinder the growth of cells, decrease cell viability, and trigger the DNA damage response and apoptosis. This is particularly intriguing considering that this plant has been utilized for ages as a culinary spice and for the treatment of diverse ailments. Infusions and oils of R. graveolens can be easily purchased commercially for medical purposes [80]. Ultimately, although Ruta graveolens exhibits potential as a natural solution for inflammation and pain, it is imperative to do additional research, including well-structured clinical studies, to thoroughly substantiate its therapeutic efficacy.

3.Conclusion

Flavonoids are significant secondary substances synthesized by plants that serve several purposes, including promoting growth and development and providing protection against stress. The recognition of the advantageous characteristics of flavonoids for human well-being has stimulated the heightened intake and fascination with the utilization of flavonoids in food processing and for medicinal purposes. R. graveolens L. is rich in flavonoids glycosides, particularly rutin compound, which is renowned for its antioxidant, anti-inflammatory, anti-cancer, and anti-viral properties. The utilization of the plant extract holds potential for treating a range of disorders and presents an opportunity for investigating alternative therapies to address these prevalent health conditions. The objective is to provide patients safer and more efficient treatment choices.

REFERENCES

[1].Nezar Cherrada, Ahmed ElkhalifaChemsa, Noura Gheraissa, Abdelmalek Zaater, Bilal Benamor, Ah med Ghania, Bouras Yassine, Abdelbasset Kaddour, Muhammad Afzaal, Aasma Asghar, Farhan Saeed & Degnet Teferi Asres (2024) Antidiabetic medicinal plants from the Chenopodiaceae family: a comprehensive overview, International Journal of Food Properties, 27:1, 194-213.

[2]. Maroyi, A., Cheikhyoussef, A., 2015. A comparative study of medicinal plants used in rural areas of Namibia and Zimbabwe. Indian J. Tradit. Know.

[3]. Lee WY, Lee CY, Kim YS, Kim CE (2019) The methodological trends of traditional herbal medicine employing network pharmacology. Biomolecules.

[4]. Aydin A, Aktay G, Yesilada E (2016) A guidance manual for the toxicity assessment of traditional herbal medicines. Nat Prod Commun 11:1763–1773.

[5]. Dai YK, Wu YB, Wen H, Li RL, Chen WJ, Tang C, Lu L, Hu L (2020) Diferent traditional herbal medicines for the treatment of gastroesophageal refux disease in adults. Front Pharmacol.

[6]. Zhai XF, Liu XL, Shen F, Fan J, Ling CQ (2018) Traditional herbal medicine prevents postoperative recurrence of small hepatocellular carcinoma: a randomized controlled study. Cancer 124:2161–2168.

[7].Qi F, Li A, Inagaki Y, Gao J, Li J, Kokudo N, Li XK, Tang W (2010) Chinese herbal medicines as adjuvant treatment during chemoor radio-therapy for cancer. Biosci Trends 4:297–307

[8]. Lee YK, Bae K, Yoo HS, Cho SH (2018) Beneft of adjuvant traditional herbal medicine with chemotherapy for resectable gastric cancer. Integr Cancer Ther 17:619–627. https://doi.org/10.1177/ 1534735417753542

[9]. Shahrajabian MH, Sun W, Soleymani A, Cheng Q (2021) Traditional herbal medicines to overcome stress, anxiety and improve mental health in outbreaks of human coronaviruses. Phyther Res 35:1237–1247.

[10]. Yu S, Wang J, Shen H (2020) Network pharmacology-based analysis of the role of traditional Chinese herbal medicines in the treatment of COVID-19. Ann Palliat Med 9:437–446.

[11]. Xu Z. Modernization: One step at a time. Nature. 2011 Dec 21;480(7378): S90-2. Erratum in: Nature. 2013 Mar 14;495(7440):270. PMID: 22190089.

[12]. Wang X. Methodology for systematic analysis of in vivo efficacy material base of traditional Chinese medicine Chinmedomics. China journal of Chinese materia medica. 2015; 40:13–17.

[13]. Shan Q.Y., Sang X.N., Hui H., Shou Q.Y., Fu H.Y., Hao M., et al. Processing and Polyherbal Formulation of Tetradium ruticarpum (A. Juss.) Hartley: Phytochemistry, Pharmacokinetics, and Toxicity. Frontiers in Pharmacology. 2020; 11:133.

[14]. Tachjian A., Maria V., Jahangir A. Use of herbal products and potential interactions in patients with cardiovascular diseases. Journal of the American College of Cardiology. 2010; 55:515–525.

[15]. Kutalek R, Prinz A (2005) African medicinal plants. Handbook of medicinal plants. CRC Press, Boca Raton, pp 97–124.

[16]. Maroyi, A., Cheikhyoussef, A., 2015. A comparative study of medicinal plants used in rural areas of Namibia and Zimbabwe. Indian J. Tradit. Knowl.

[17]. Jones D. Rutaceae. In: The Flora of Sabah and Sarawak. 5th ed., Kuala Lumpur: Ampang Press Sdn; 1995:351-401. 2. Bently. R, Trimen H. Medicinals Plants. 1st ed., New Delhi: Asiatic Publishing House; 2004:44 serial number.

[18]. Bently. R, Trimen H. Medicinals Plants. 1st ed., New Delhi: Asiatic Publishing House; 2004:44 serial number.

[19]. W. Dymock CJHW, D. Hooper. Pharmacographia Indica: A History of the Principal Drugs of Vegetable Origin. 3rd ed., New Delhi: Srishti Book Distributors; 2005:249-252.

[20]. Anonymous. The Wealth of India. 5th ed., New Delhi: Council of Scientific and Industrial Research; 2004:94-96.

[21]. Kuzovkina I, Al'terman I, Schneider B. Specific accumulation and revised structures of acridone alkaloid glucosides in the tips of transformed roots of Ruta graveolens. Phytochemistry 2004;65:1095-100.

[22]. Milesi S MB, Gontier E, F Bourgaud, Guckert A. Ruta graveolens L.: a promising species for the production of furanocoumarins. Plant Sci.161: 2001:189-199.

[23]. Yazbek, P.B.; Tezoto, J.; Cassas, F.; Rodrigues, E. Plants used during maternity, menstrual cycle and other women's health conditions among Brazilian cultures. J. Ethnopharmacol. 2016, 179, 310–331.

[24]. Conway, G.A.; Slocumb, J.C. Plants used as abortifacients and emmenagogues by Spanish New Mexicans. J. Ethnopharmacol. 1979, 1, 241–261.

[25]. Pollio, A.; De Natale, A.; Appetiti, E.; Aliotta, G.; Touwaide, A. Continuity and change in the Mediterranean

medical tradition: Ruta spp. (rutaceae) in Hippocratic medicine and present practices. J. Ethnopharmacol. 2008, 116, 469–482.

[26]. Haesen, J.P.; Vörding, J.G.; Kho, K.F. Isolation and identification of xanthotoxin from the underground partsof Ruta graveolens. Planta Med. 1971, 19, 285–289.

[27]. Asgharian S, Hojjati MR, Ahrari M, Bijad E, Deris F, Lorigooini Z. *Ruta graveolens* and rutin, as its major compound: investigating their effect on spatial memory and passive avoidance memory in rats. Pharm Biol. 2020 Dec;58(1):447-453. doi: 10.1080/13880209.2020.1762669. PMID: 32432948; PMCID: PMC7301720.

[28]. Izadpanah F, Arab F, Zarghami A, Bijani A, Kazemi S, Moghadamnia AA.. 2017. The effect of lamotrigine on learning in mice using the passive avoidance model. *Epilepsy Behav*. 69:1–6.

[29]. Kanika patel , Dinesh Kumer Patel. January 2019 (Bioactive Food as Dietary Interventions for Arthritis and Related Inflammatory Diseases) (pp.457-479).

[30]. Asgharian S, Hojjati MR, Ahrari M, Bijad E, Deris F, Lorigooini Z. *Ruta graveolens* and rutin, as its major compound: investigating their effect on spatial memory and passive avoidance memory in rats. Pharm Biol. 2020 Dec;58(1):447-453. doi: 10.1080/13880209.2020.1762669. PMID: 32432948; PMCID: PMC7301720.

[31] G. Donadio, F. Mensitieri, V. Santoro et al., “Interactions with microbial proteins driving the antibacterial activity of flavonoids,” Pharmaceutics, vol. 13, no. 5, p. 660, 2021.

[32] A. Roy, S. Datta, K. S. Bhatia, Bhumika, P. Jha, and R. Prasad, “Role of plant derived bioactive compounds against cancer,” South African Journal of Botany, 2021.

[33] M. S. D'Arcy, “A review of biologically active flavonoids as inducers of autophagy and apoptosis in neoplastic cells and as cytoprotective agents in non-neoplastic cells,” Cell Biology International, 2022.

[34] F. Perez-Vizcaino and C. G. Fraga, “Research trends in flavonoids and health,” Archives of Biochemistry and Biophysics, vol. 646, pp. 107–112, 2018.

[35] R. Luthra, A. Roy, S. Pandit, and R. Prasad, “Biotechnological methods for the production of ginsenosides,” South African Journal of Botany, vol. 141, pp. 25–36, 2021.

[36]. Al-Ishaq RK, Abotaleb M, Kubatka P, Kajo K, Büsselberg D. Flavonoids and their anti-diabetic effects: Cellular mechanisms and effects to improve blood sugar levels. Biomolecules. 2019 Sep 1; 9(9).

[37]. Hamid HK, Obaid MA. Role of Quercetin Flavonoid as Antidiabetic: A Review. International Journal of Drug Delivery Technology. Dr. Yashwant Research Labs Pvt. Ltd. 2021; 11:1495-500.

[38] S. Kaur and A. Roy, “A Review on the nutritional aspects of wild edible plants,” Current Traditional Medicine, vol. 7, no. 4, pp. 552–563, 2021.

[39].Gravot A, Larbat R, Hehn A, Lievre K, Gontier E, Goergen JL, Bourgaud F. Cinnamic acid 4-hydroxylase mechanism-based inactivation by psoralen derivatives: cloning and characterization of a C4H from a psoralen producing plant—Ruta graveolens—exhibiting lowsensitivity to psoralen inactivation. Archives of Biochemistry and Biophysics. 2004 Feb 1;422(1):71-80.

[40]. Meepagala KM, Schrader KK, Wedge DE, Duke SO. Algicidal and antifungal compounds from the roots of Ruta graveolens and synthesis of their analogs. Phytochemistry. 2005 Nov 1;66(22):2689-95.

[41].Hale AL, Meepagala KM, Oliva A, Aliotta G, Duke SO. Phytotoxins from the leaves of Ruta graveolens. Journal of agricultural and food chemistry. 2004 Jun 2;52(11):33459.

[42]. Michael A, Prenzler PD, Emilios P, Suzanne M, Kevin R. Methods for testing antioxidant activity. Analyst 2002;127(1):183-98.

[43]. Lien A, Hua H, Chuong P. Free radicals, antioxidants in disease and health. Int J Biomed Sci 2008;4(2):89-96.

[44]. Pirouzpanah S, Rashidi MR, Delazar A, Razavieh SV, Hamidi A. Inhibitory effects of *Ruta graveolens* L. Extract on guinea pig liver aldehyde oxidase. Chem Pharm Bull (Tokyo) 2006;54(1):9-13.

[45].Vismruti Rathod, Ms. Krupa Vyas, & Dr. Pragnesh Patani. (2023). “A COMPARATIVE STUDY OF ANTI- INFLAMMATORY AND ANALGESIC PROPERTIES OF PLANT RUTA GRAVEOLENS AND ALLOPATHIC MEDICINE”. *Journal of Population Therapeutics and Clinical Pharmacology*, *30*(19), 2012–2022.

[46]. Mitra Noori1,♥ , Mehrana Jafari1 , Hanie Azimi2 , Mehdi Node-Farahani 1 N U S A N T A R A B I O S C I E N C E Issn: 2087-3948 Vol. 11, No. 1, Pp. 23-29 E-Issn: 2087-3956 May 2019.

[47]. Farid O, Hebi M, Ajebli M, Hidani AE, Eddouks M. Antidiabetic effect of Ruta montana L. in streptozotocin-induced diabetic rats. J Basic Clin Physiol Pharmacol. 2017 May 1;28(3):275-282. doi: 10.1515/jbcpp-2016-0030. PMID: 28121617.

[48]. Pandhare RB, Sangameswaran B, Mohite PB, Khanage SG. Antidiabetic Activity of Aqueous Leaves Extract of Sesbania sesban (L) Merr. in Streptozotocin Induced Diabetic Rats. Avicenna J Med Biotechnol. 2011 Jan;3(1):37-43. PMID: 23407749; PMCID: PMC3558175

[49]. Aslan M, Orhan DD, Orhan N, Sezik E, Yesilada E. In vivo antidiabetic and antioxidant potential of Helichrysum plicatum ssp. plicatum capitulums in Streptozotocin-induced-diabetic rats. *J Ethnopharmacol.* 2007;109(1):54–59.

[50]. Yadav JP, Saini S, Kalia AN, Dangi AS. Hypoglycemic and hypolipidemic activity of ethanolic extract of Salvodora oleoides in normal and alloxaninduced diabetic rats. *Indian J Pharmacol.* 2008;40(1):23–27.

[51]. R. Vinayagam and B. Xu, "Antidiabetic properties of dietary flavonoids: a cellular mechanism review," Nutrition & metabolism, vol. 12, no. 1, pp. 1–20, 2015.

[52] B. A. Graf, P. E. Milbury, and J. B. Blumberg, "Flavonols, flavones, flavanones, and human health: epidemiological evidence," Journal of Medicinal Food, vol. 8, no. 3, pp. 281–290, 2005.

[53] T. T. Cushnie and A. J. Lamb, "Antimicrobial activity of flavonoids," International Journal of Antimicrobial Agents, vol. 26, no. 5, pp. 343–356, 2005.

[54] R. Jarial, S. Thakur, M. Sakinah et al., "Potent anticancer, antioxidant, and antibacterial activities of isolated flavonoids from Asplenium nidus," Journal of King Saud University-Science, vol. 30, no. 2, pp. 185–192, 2018.

[55] D. Tungmunnithum, A. Thongboonyou, A. Pholboon, and A. Yangsabai, "Flavonoids and other phenolic compounds from medicinal plants for pharmaceutical and medical aspects: an overview," Medicine, vol. 5, no. 3, p. 93, 2018.

[56] M. D. L. Aviram, L. Dornfeld, M. Rosenblat et al., "Consumption of pomegranate juice reduces oxidative stress, atherogenic modifications to LDL, and platelet aggregation: studies in humans and mice deficient in atherosclerotic apolipoprotein E," Am Journal of Clinical Nutrition, vol. 71, no. 5, pp. 1062– 1076, 2000.

[57] T. Henriksen, E. M. Mahoney, and D. Steinberg, "Enhanced macrophage degradation of low-density lipoprotein previously incubated with cultured endothelial cells: recognition by receptors for acetylated low density lipoproteins," Proceedings of the National Academy of Sciences, vol. 78, no. 10, pp. 6499– 6503, 1981.

[58] Rethy B, Zupko I, Minorics R, Hohmann J, Ocsovszki I, Falkay G. Investigation of cytotoxic activity on human cancer cell lines of arborinine and furanoacridones isolated from Ruta graveolens. Planta medica. 2007 Jan;73(01):41-8.

[59]. AL-Ishaq, R.K.; Abotaleb, M.; Kubatka, P.; Kajo, K.; Büsselberg, D. Flavonoids and Their Anti-Diabetic Effects: Cellular Mechanisms and Effects to Improve Blood Sugar Levels. *Biomolecules* 2019, *9*, 430.

[60]. Menezes R, Matafome P, Freitas M, García-Conesa MT. Updated Information of the Effects of (Poly)phenols against Type-2 Diabetes Mellitus in Humans: Reinforcing the Recommendations for Future Research. Nutrients. 2022 Aug 30;14(17):3563. doi: 10.3390/nu14173563. PMID: 36079821; PMCID: PMC9460145.

[61]. Pétriacq P, López A, Luna E. Fruit Decay to Diseases: Can Induced Resistance and Priming Help? Plants (Basel). 2018 Sep 21;7(4):77. doi: 10.3390/plants7040077. PMID: 30248893; PMCID: PMC6314081.

[62]. Nikaido H. Multidrug resistance in bacteria. Annu Rev Biochem. 2009; 78:119-46.

[63]. Vaou N, Stavropoulou E, Voidarou C, Tsigalou C, Bezirtzoglou E. Towards Advances in Medicinal Plant Antimicrobial Activity: A Review Study on Challenges and Future Perspectives. Microorganisms. 2021 Sep 27;9(10):2041.

64. Pavić V, Flačer D, Jakovljević M, Molnar M, Jokić S. Assessment of Total Phenolic Content, In Vitro Antioxidant and Antibacterial Activity of *Ruta graveolens* L. Extracts Obtained by Choline Chloride Based Natural Deep Eutectic Solvents. Plants (Basel). 2019 Mar 18;8(3):69.

[65]. Magden J, Kääriäinen L, Ahola T. Inhibitors of virus replication: recent developments and prospects. Appl Microbiol Biotechnol. 2005 Mar;66(6):612-21.

[66]. Basak D, Arrighi S, Darwiche Y, Deb S. Comparison of Anticancer Drug Toxicities: Paradigm Shift in Adverse Effect Profile. Life (Basel). 2021 Dec 29;12(1):48.

[67]. Ullah A, Munir S, Badshah SL, Khan N, Ghani L, Poulson BG, Emwas AH, Jaremko M. Important Flavonoids and Their Role as a Therapeutic Agent. Molecules. 2020 Nov 11;25(22):5243.

[68]. G MS, Swetha M, Keerthana CK, Rayginia TP, Anto RJ. Cancer Chemoprevention: A Strategic Approach Using Phytochemicals. Front Pharmacol. 2022 Jan 13; 12:809308.

[69]. Mahmoud, E.A.; Elansary, H.O.; El-Ansary, D.O.; Al-Mana, F.A. Elevated Bioactivity of *Ruta graveolens* against Cancer Cells and Microbes Using Seaweeds. *Processes* 2020, *8*, 75.

[70]. Preethi KC, Kuttan G, Kuttan R. Anti-tumour activity of Ruta graveolens extract. Asian Pac J Cancer Prev. 2006 Jul-Sep;7(3):439-43.

[71]. Rasola A, Bernardi P. The mitochondrial permeability transition pore and its adaptive responses in tumor cells. Cell Calcium. 2014 Dec;56(6):437-45. doi: 10.1016/j.ceca.2014.10.003. Epub 2014 Oct 16.

[72]. Fadlalla K, Watson A, Yehualaeshet T, Turner T, Samuel T. Ruta graveolens extract induces DNA damage pathways and blocks Akt activation to inhibit cancer cell proliferation and survival. Anticancer Res. 2011 Jan;31(1):233-41. PMID: 21273604; PMCID: PMC3124362.eration and survival through multiple targets.

[73]. Karp JC, Sanchez C, Guilbert P, Mina W, Demonceaux A, Curé H. Treatment with Ruta graveolens 5CH and Rhus toxicodendron 9CH may reduce joint pain and stiffness linked to aromatase

inhibitors in women with early breast cancer: results of a pilot observational study. Homeopathy. 2016 Nov;105(4):299-308.

[74]. Homeopathy. 2016 Nov 1;105(4):299-308. 41.Ratheesh M, Sindhu G, Helen A. Anti-inflammatory effect of quinoline alkaloid skimmianine isolated from Ruta graveolens L. Inflammation research: official journal of the European Histamine Research Society...[et al.]. 2013 Apr;62(4):367-76.

[75]. Joo SW, Lee BC, Lee J, Seo GH. Risk of Breast Cancer in Association with the Use of Second-generation Antipsychotics. Clin Psychopharmacol Neurosci. 2022 Nov 30;20(4):675-684.

[76]. Misty Prince, Cheryl T. Campbell, Taylor A. Robertson, Amy J. Wells, Heather E. Kleiner, naturally occurring coumarins inhibit 7,12-dimethylbenz [*a*] anthracene DNA adduct formation in mouse mammary gland, *Carcinogenesis*, Volume 27, Issue 6, June 2006, Pages 1204–1213,

[77]. Kleiner HE, Vulimiri SV, Starost MF, Reed MJ, DiGiovanni J. Oral administration of the citrus coumarin, isopimpinellin, blocks DNA adduct formation and skin tumor initiation by 7,12-dimethylbenz[a]anthracene in SENCAR mice. Carcinogenesis. 2002 Oct;23(10):1667-75.

[78]. Steck W, Bailey BK, Shyluk JP, Gamborg OL. Coumarins and alkaloids from cell cultures of Ruta graveolens. Phytochemistry. 1971;10(1):191-4. doi: 10.1016/S0031-9422(00)90269-3.

[79]. Prince M, Campbell CT, Robertson TA, Wells AJ, Kleiner HE. Naturally occurring coumarins inhibit 7, 12-dimethylbenz [a] anthracene DNA adduct formation in mouse mammary gland. Carcinogenesis. 2006;27(6):1204-13.

[80]. Roy A, Khan A, Ahmad I, Alghamdi S, Rajab BS, Babalghith AO, Alshahrani MY, Islam S, Islam MR. Flavonoids a Bioactive Compound from Medicinal Plants and Its Therapeutic Applications. Biomed Res Int. 2022 Jun 6; 2022:5445291.