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SCHOOL OF MEDICAL AND ALLIED SCIENCES

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DEPARTMENT OF PHARMACY

GALGOTIAS UNIVERSITY, GREATER NOIDA, G.B. NAGAR (U.P)

DEPARTMENT OF PHARMACY



CERTIFICATE

This is to certify that the work contained in this project on **Sources, Properties and Pharmacological Effects of Quercetin** submitted in partial fulfilment for the academic requirement in the degree of Bachelor of Pharmacy is the original work carries out by **ANKIT** during the academic year 2020–21, under the guidance of **MR. RISHABHA MALVIYA (Assistant Professor)**. The work is completed and ready for evaluation in partial fulfilment for the award of bachelor of pharmacy under Galgotias University Greater Noida during the academic year 2020-21.

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DECLARATION

The project report **SOURCES, PROPERTIES AND PHARMACOLOGICAL EFFECTS OF QUERCETIN** entitled is the compilation work of **MR. ANKIT** under supervision of **MR. RISHABHA MALVIYA** Assistant Professor **Department of Pharmacy, GALGOTIAS UNIVERSITY Greater Noida U.P India**. All pictures, Figures and information used in project are taken from various sources are true and best of my knowledge.

Name and signature of candidate

(ANKIT)

ENROLLMENT No. 1712102013

DEDICATION

I dedicate this to my guider teacher MR. RISHABHA MALVIYA (Assistant professor) who taught me everything about this project and taught me the basics rules of life that are very useful and important for a person to live a healthy life. Sir taught that never too late to start a thing and achieve your goals. Sir you and your thoughts really motivates me in my life and my carrier so sir thank you for guiding me.

Acknowledgement

I Would like to express my special thanks of gratitude to my project guide **MR. RISHABHA MALVIYA** as well as our Dean **MR. PRAMOD KUMAR SHARMA** who gave me the golden opportunity to do this wonderful project on the topic **SOURCES, PROPERTIES AND PHARMACOLOGICAL EFFECTS OF QUERCETIN** , which also helped me in doing a lot of research and I come to know about so many new things.

I new really thankful them.

Secondly I would also like a thank my friends who helped me a lot in finishing this project within the limited It helped me increase my knowledge and skills.

ANKIT

Sources, Properties and Pharmacological Effects of Quercetin

Abstract: The present review aims to describe an overview of quercetin with its various pharmacological effects. Quercetin is used as antioxidant, anticancer, antibacterial and antimicrobial, anti-inflammatory, antidiabetic, antihypertensive, antifungal, anti-allergic and antiproliferative agents which are described in the manuscript. It is mainly obtained from the plant resources which is also described in the manuscript. The manuscript also focuses to describe the various studies related to quercetin which shows the various pharmacological activity. It is concluded from the study that quercetin has shown an efficacious effect on various diseases.

Keywords: Quercetin; pharmacological effect; anti-inflammatory; antifungal; anticancer; natural product

Introduction:

Quercetin has various synonyms such as Sulfotransferase, flavonol 3'Flavonol, 3'-sulfotransferase, PAPS: flavonol 3-sulfate 3'-sulfotransferase [1] It has molecular formula w molar mass: 302.2 g mol⁻¹. Quercetin have 1799 kg m⁻³ density with 6.31 pK_a value [2]. It has a 316⁰C melting point. It has a slightly yellow color found in powder form [3]. It is practically insoluble in water and soluble in aqueous alkaline solutions [4, 5].

Quercetin is a natural flavonoid that is universal. It has many pharmacological properties which help in various health related issues such as gastrointestinal disorders, inflammatory problems and immune related issue [6]. Flavonoid contains a group of polyphenols. Quercetin is found in many varieties of fruits and vegetables. Quercetin is easily extractable and detectable. Such low-subatomic weight constituents are typically delivered through greens for safety in opposition to pests & illnesses, towards guidelines of development, & as essence, color and smell. It has the molecular formula C₁₅H₁₄O₉ and its structure is shown in Figure 1 [7, 19].

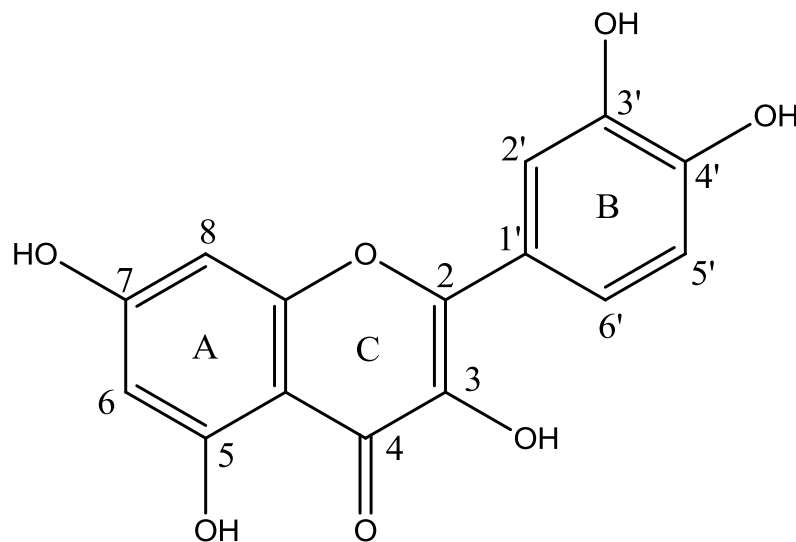


Figure 1. Structure of Quercetin

A huge number of the public is interested in herbal products and formulation observed. Accordingly, major products developed with natural and herbal remedies. Quercetin is not formed in the human body. Quercetin has high efficacy in the treatment of cancer leafy greens contain a higher amount of quercetin such as Kale and broccoli [6]. Flavonols like Quercetin (primarily as quercetin glycosides) are widely distributed in plants. They are found in different food products, including apples, berries, Brassica vegetables, shallots, tea, capers, grapes, onions and tomatoes, as well as many seeds, nuts, flowers, barks, and leaves. It is also found in medicinal plants, including *Ginkgo biloba*, *Camellia sinensis*, *Hypericum perforatum*, and *Sambucus canadensis*. In a study, it was found that organically grown tomatoes had 79% more quercetin than chemically grown fruit. In red onions, higher concentrations of quercetin occur in the outermost rings and the part closest to the root, the latter being the part of the plant with the highest concentration. Quercetin is present in various kinds of honey from different plant sources [8]. Different sources of quercetin are shown in figure 2.

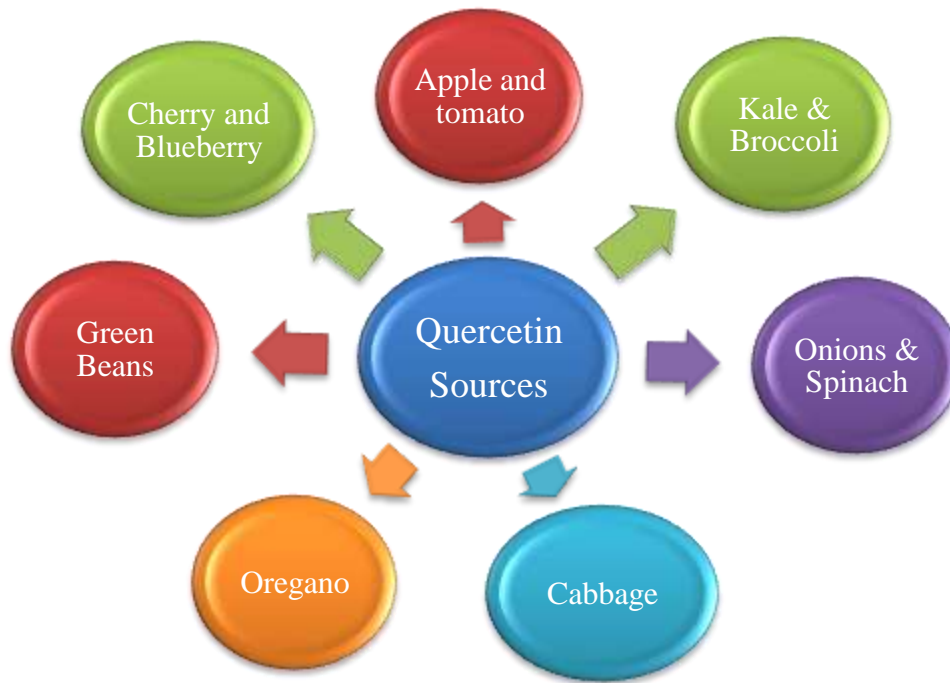


Figure 2. The schematic diagram shows the different sources of quercetin

Extraction process of quercetin is summarized in figure 3.

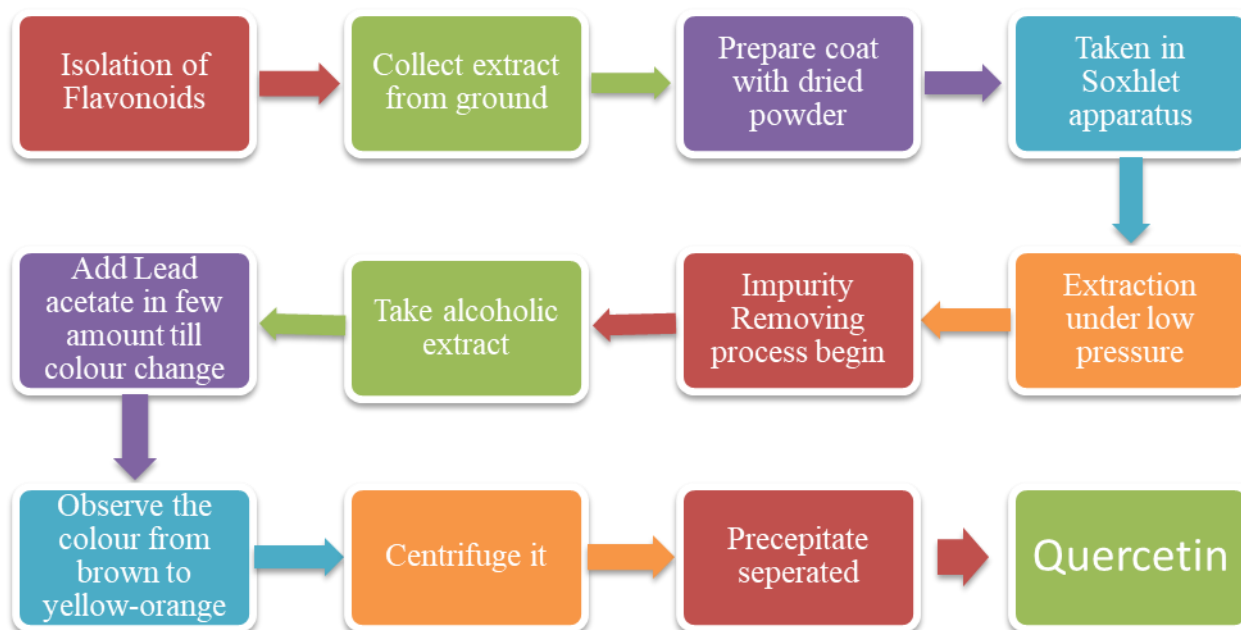


Figure 3. Schematic diagram of quercetin extraction process.

Grape Pomaces were obtained by fermenting the mixture of grape varieties and by maintaining the temperature at 20° C before use. It is a good source of quercetin. Grape Pomaces extracted by different methods are shown in Table 1 [9].

Table 1. Phenolic compounds extracted from species of grape pomace are shown in the table

Method of extraction	Extraction of liquid-fluid solvent	Compound having phenol
C₂H₅OH (Ethanol)	CHCl ₃ (Chloroform)	C ₁₅ H ₁₄ O ₉ (Quercetin)
C₂H₅OH (Ethanol)	C ₄ H ₈ O ₂ (Ethyl acetate)	C ₁₅ H ₁₄ O ₉ (Quercetin)
CH₃OH (Methanol)	C ₆ H ₁₄ (Hexane)	C ₁₅ H ₁₄ O ₉ (Quercetin)
CH₃OH (Methanol)	CHCl ₃ (Chloroform)	C ₁₅ H ₁₄ O ₉ (Quercetin)
CH₃OH (Methanol)	C ₄ H ₈ O ₂ (Ethyl acetate)	C ₁₅ H ₁₄ O ₉ (Quercetin)
Soxhlet	CH ₃ OH (Methanol)	C ₁₅ H ₁₄ O ₉ (Quercetin)
Soxhlet	CH ₃ OH (Methanol)	Gallic acid

Pharmacological activities of Quercetin include various activities such as antiulcer [5] anticancer [10], antioxidant, in osteoporosis, depression, anxiety, lung and cardiovascular diseases [11], as a dietary supplement [12], in Alzheimer's disease [13], ant-diabetic [14], as chemopreventive agent [15]. The pharmacological activities of quercetin are also summarized in figure 4.

Figure 4. The schematic diagram represents the pharmacological activities of quercetin.

1. • ANTIOXIDANT
2. • ANTICANCER
3. • ANTIBACTERIAL & ANTIMICROBIAL
4. • ANTI INFLAMMATORY
5. • ANTIDIABETIC
6. • ANTIHYPERTENSIVE
7. • ANTIFUNGAL
8. • ANTIALLERGIC
9. • ANTIPROLIFERATIVE

Quercetin is mainly found in the bark of *Quercus tinctoria* found in the family of Hippocastanaceae. During extraction, impurities can be removed by lead acetate solution with the help of centrifugation. Quercetin containing plants can be used in cancer treatment [16]. The various activity of quercetin is described in detail below.

Antioxidant activity:

Quercetin has a more efficient ability of antioxidant property so it can protect the body against much reactive oxygen during oxygen metabolism [17]. Through the reactive oxygen species (ROS), cellular death can cause which have to protect by developing an antioxidant line of defence system [18]. LDL oxidation level reduces by quercetin therefore atherosclerosis and risk of heart diseases are being reduced [19] [20]. Quercetin has the ability to clearance of reactive oxygen species (ROS). Inhibitory effect of in-vivo in opposition to tertiary butylhydroperoxide convinced lipid peroxidation in sperm cell of a human shown in the report of quercetin [21] and various functions with cardiovascular system [22].

In the biochemical signaling pathway, quercetin has great involvement [17]. The better antioxidant effect is shown in opposition to oxidative stress which is caused through the streptozotocin affected diabetes mellitus mostly in rats. Better antioxidant & equalizer in polyethylene has also been reported in quercetin property [21]. *In-Vitro* antioxidant activity shows by glucuronic acid & sulfates [23]. Antioxidants terminate lipid peroxidation [17].

Quercetin has been used in chelation therapy as a chelating agent in treatment for removal of hazardous metallic ions because quercetin & cadmium aggregates have shown greater stability constant [21]. Glycoside has more antioxidant activity. Quercetin antioxidant properties also contribute to the activities of free radicals which is present in the environment. Conjugate metabolite of quercetin can prevent damage to membranes of RBC due to smoking [7] [17] [23].

Quercetin has a better scavenger of O₂⁻ than nitrous oxide (NO) in an increase of O₂⁻ within smooth muscles of blood vessels. Hydroxyl polyphenolic structure provides favorable anti-oxidant chemical [7] [24]. Flavonoids activity reported that to suppress the expression of NOS (nitric oxide synthase) without suppressing its activity. By restricting the activity of inducible NOS, reduction of ischemia-reperfusion injury is shown. Quercetin acts by targeting unique molecules [7] [24].

The contribution of hydrogen atoms to the alpha-tocopheryl radical in flavonoids is a potential Pro-oxidant. Quercetin can produce both antioxidant and pro-oxidant effects. Through quercetin, glutathione promotes damage to DNA [7]. It reduces the risk of chronic diseases related to oxidative stress [17]. The increased antioxidant effect showed when quercetin or catechin & chlorpyrifos induced groups in rats [25].

Anticancer activity:

During this time cancer requires new therapeutics or chemical entities for its treatment. Quercetin has the potency of an anticancerous agent in different cancer cells. Quercetin is also capable of preventing cancer which is produced by oxidative stress. It has radical scavenging potential. Enhancing immune responses against breast cancer growth when the combination of quercetin and intratumoral doxorubicin injection [21]. In the first phase clinical trial, antitumor activity evidence was observed in double-blind, crossover, placebo-controlled and randomized trials [17]. Reactive Oxygen and nitrogen species (ROS/RON) show carcinogenic effects and may cause DNA damage, alter cell signaling pathways [18].

Many clinical trials, *in vivo*, *in vitro* studies evidence and investigations show plant based diets have more protective effects in Cancer. Quercetin has properties of preventing ROS/RON. It has also been reported that quercetin can inhibit angiogenesis. In Cancer, pathological and unregulated angiogenesis occurs. The proper mechanism is unclear of the anti-angiogenic effect of flavonoids [17, 18]. Assertion of the cell-cycle gene, up regulation of the genes expressing the suppression of tumor cells & down regulation of the expression of oncogenes in cell lines of prostate cancer, can be inhibited by quercetin. Also, expression of the androgen receptor protein at the transcription level phase was diminished by quercetin analog [25].

Quercetin has low bioavailability in plasma so not easily explain *in vivo* anti-cancerous effect [14]. Many of the anticancer drugs produce mitochondrial toxicity and bring out the reactive oxygen(O) species which leads to the death of cancer cells. In the simulation of molecular dynamics, Joshi et. al. studied the action & effect of anticancer, antioxidant and anti-inflammatory action in 2-modified groups i.e Quercetin-Cl & Quercetin-OCH₃ in the compound of quercetin [25]. There is proof that efficacy in an antitumor agent is identified with the natural tendency of the marked tumor cells to react to these antitumor agents by apoptosis [26].

It's been demonstrated that best Quercetin activity is in blood, cerebrum, lungs, uterus, & salivary organ malignancy as great as upon melanoma with the cytotoxic action a lot enhanced in the

forceful cell than in sluggish developing cell recommending that the with the most destructive cells are one mainly focused [17]. In cancer treatment failure main cause is multidrug resistance (MDR) due to it involved the increased activity of the Adenosine Tri Phosphate-binding family transporters. In the function of the dendritic cells, quercetin acts as an immunosuppressive effect. In many investigations, quercetin was reported as having anti-proliferative effects in numerous cell types while studying the no. of animal pharmacokinetic models and cell lines of human cancer [25].

Gibellini *et al.* found that the strong anticancer activity in the quercetin due to the activity of chemoprotective by apoptosis & metastasis. Quercetin shows its anticancer activity by a different mechanism of action as cell signaling, binding to cell reporters & proteins, & inhibition of the enzymes responsible for the carcinogenic activation [6]. From mitochondrial oxidative phosphorylation, the increased requirements for ATP, generation of the free oxygen(O) radicals that create the oxidative stress which leads to cell death. Due to this response, the cancerous cells utilize glucose (C₆H₁₂O₆) as an energy source [16]. Mice bear A549 tumor strain shows decreased cancer cell growth within the In-Vivo condition after inducing quercetin through injection [27]. Table 2 shows the effect of quercetin on apoptosis on the different tumor cell lines and their mechanism.

Table 2. Quercetin’s effect on apoptosis in the different tumor cell lines and its mechanism.

Cancer cell-Type	Signaling cell-Pathway	Mechanism
Lung Cancer	AKT-survivin	Increased DR5 Decreased Survivin [27]
Lymphoma Cell	m-TOR & STAT3	Decreased c-FLIP, cMyc [28]
Breast Cancer	STAT3	Increased Caspase-3-8, p53, p21 [29]
Ovary Cancer	Aldehyde dehydrogenase, transcription factor	Decreased Cyclin-D1, phosphohistone- H3, Dna-PK. Increased p21 [30]

Antibacterial & Antimicrobial activity:

The better effect in the biological suppression shows by quercetin. Its mechanism was shown in four terms (i) resistance & damage of the cell envelope, (ii) stops or breaks off bacterial adherence, (iii) blocks the synthesis of nucleic acid (iv) inhibits pathogen forming biofilms. Wang *et al.* reveal the capability of the quercetin to destruct the cytoderm in *E-coli*. Nalita *et al.* demonstrate that streptococcus mutants strains could be remarkably inhibited by quercetin by inhibiting the acid production & the formation of the biofilm. In the study quercetin shows resistance to the biofilm in its composition and structure. [32].

To singular viruses, the quercetin antiviral effect is not restricted [19]. Quercetin shows antimicrobial activity in the preservation and storage of fattening lamb's meat. Microbial growth has reported a decrease upon freezing [21]. The disk diffusion method helps to investigate antimicrobial or antibacterial activity in quercetin extract [33]. The mutagenic action of quercetin in microbes isn't evidence of genetic hazard to higher organisms [34]. On Fungi, quercetin has also significant inhibitory activity due to the involvement of cell wall and cell membrane destruction [35].

Quercetin also shows its efficacy against *Lactobacillus casei var shirota* [6]. In most experiments quercetin was found as an ideal inhibitory activity on the growth & development of the pathogens like *P. aeruginosa*, *Staphylococcus aureus*, *Salmonella* strains, *E-coli* and *Aspergillus* strains [21].

Anti-inflammatory activity:

In an, *in vivo* study, inflammatory genes show a reduction in expression by using quercetin enriched diet reported in mice [21]. A high amount of NO₂ produced by infiltrated inflammatory cells, which is severe in killing infected microorganisms for safety from infection [24]. Quercetin shows an anti-inflammatory effect by reducing the neuropathic (migraine) pain by inhibiting the signaling pathway of Toll-like protein receptor [27]. In Graves' orbitopathy treatment, quercetin has great potential activity as an anti-inflammatory agent [17].

This is more powerful as an anti-histaminic in preventing asthma attacks and allergic reactions. Quercetin is additionally a powerful inhibitor of leukotriene B₄ development in leukocytes [19]. Quercetin's anti-inflammatory effect & its glycoside derivative found ineffective against topical inflammation due to its lower absorption in the skin surface. Pentamethylether derivative has very good absorption properties with skin route [21]. Knaapen *et al.* found that during chronic pulmonary inflammation, H₂O₂ is released from inflammatory cells [36].

The anti-inflammatory activity appears also due to subsequent inhibition of the inflammatory mediators, with include leukotrienes and prostaglandins. Mast cells and basophils contribute to the effect of anti-inflammation through inhibition of histamine release [20]. No effect of inflammatory agents on healthy human volunteers reported while performing *in vivo* and *ex vivo* studies [21]. Enzymes along with the β -glucuronidase effect could release beneath specific physiologic circumstances like neoplasm and inflammation [37].

Antidiabetic activity:

Now-a-days renewed interest is shown in the use of plant related compounds as anti diabetic composites. In the flavonol category, they are phenolic compounds that occur naturally which are broadly divided in plants [38]. A low level of laser treatment and quercetin application together was appeared to improve cuts and puncture healing in diabetic and antidiabetic rats, while contrasting their impact [27]. Quercetin reported through several studies that it obstructs oxidative

harm affected by the acrylamide, brain harm due to radiation, nerve damage on the retina of diabetic rat [6].

In the study, quercetin was observed as an inhibitor of the aldose reductase enzyme, which helps in the conversion of glucose to sorbitol. Other problems occurred in peoples such as diabetic cataracts, neuropathy, nephropathy and retinopathy due to sorbitol buildup [18]. β cells influenced through numerous therapeutical and catalytic agents prompting small inflammations creating glucocorticoids. DNA replication occurs in the β cells & β cell recovery turns to be cultivated [38].

Braga *et al.* investigated the quercetin's effect on the placental and fetal and maternal reproductive capacity development in diabetic rats [39]. Quercetin brought about an expansion of islet cells in animals having normal glucose levels, however, it brought down glucokinase (phosphorylation of glucose to glucose-6-phosphate) activity and expanded blood cholesterol & triglycerides level in normoglycemic animals [38, 40]. Furthermore, anti-diabetic efficacy shows when quercetin binds to aldose reductase [24].

Antihypertensive activity:

The major risk factor is high blood pressure for developing these diseases. Lifestyle is also a reason related to health. A study shows that intake of fruits & vegetables helps to reduce hypertension. Daily basis physical exercise, reduction of smoking and alcohol intake helps to gain better health. [42]. Due to low or decrease of antioxidant capacity, an extremely increased oxidative stress observed in pregnancy induced hypertension. ROS (Reactive oxygen species) plays an important role in hypertension, diabetes, atherosclerosis, heart failure, and ischaemic heart diseases. In the animal studies review, quercetin shows increase drug bioavailability in most of the drugs including anticancer drugs, antihypertensive drugs, a drug used in heart failure, the drug to the treatment of angina pectoris and etc. [39, 43, 44].

Methyldopa combination with quercetin could diminish the adverse effect. The same result is expected in the combination of quercetin and some antihypertensive drugs (nitrendipine, nifedipine, hydralazine, labetalol) [39]. Also studied the quercetin's effect on the elevated B.P observed in the metabolic syndrome which is the condition of obesity and type 2 diabetes [42]. In the quercetin's antihypertensive effect, it has been documented to increase the NO (nitric oxide) availability affected by increased NOS (nitric oxide synthase) effect [45].

In pregnancy-induced hypertension, many patients suffer from cardiovascular diseases and need better and effective treatment. The national high blood pressure education program categorizes pregnancy hypertension into four groups [39]. Yukiko *et al.* did not found any effect of quercetin on nitric oxide synthase (NOS) activity in rat's vascular tissue. But they found one report of quercetin on SHR (Spontaneously hypertensive rat) in antihypertensive effect [41].

Duarte *et al.* reported quercetin's anti-hypertensive activity in SHR (Spontaneously hypertensive rat) by oral dose [41, 44]. Clinical trials of pure quercetin were analyzed on the healthy volunteers for cardiovascular risk factor [42] Better therapeutic benefit in heart related or cardiovascular diseases by quercetin and wine polyphenols [45]. A study shows in cultured macrophages, quercetin glucuronides could be deconjugated *in vitro*. In SHR (Spontaneously hypertensive rat) oral quercetin helps to reduce blood pressure by almost 30% [46].

Antifungal activity:

Quercetin's synthetic property showed its antifungal activity against the *Candida albicans* cultures. When quercetin is administered intravenously, it disappears rapidly from the plasma. It means quercetin is metabolized & excretion in the urine occurs immediately without accumulation/retention in tissues & cells. Quercetin-CF₃ has a high lipophilic trifluoromethyl group, which can increase the amphiphilicity of the structure. Chemical or substance functional group modification change of rutin to create quercetin-CF₃* involved by an extensive expansion in the antifungal property [47].

Minimal activity shows biofilms of candida species when analog of gallic acid and quercetin combination provided [48]. Quercetin demonstrates antifungal function to sensitizing the probability of the fluconazole resistant *Candida albicans* separates to fluconazole [49].

Munoz *et al.* found that in fungal separate & culture medium condition study, Botrytis. cinerea fungal strain G29 obtained from naturally infected grapes (*V. vinifera*) & grown & facilitated on the prepared (malt-yeast extract agar slant at the temp. 4° C). The antifungal activity shows *in vitro* with the different phenolic compounds and extracts [9]. In a study, rutin and quercetin don't show antifungal effects against C.neoformans alone. The improved antifungal effect shows when these compounds are associated with amphotericin B [50]. Quercetin and kaempferol both show their antifungal effect against planktonic cells (cryptic species) [51].

Kaempferol & quercetin shown a great antibiofilm effect, particularly vs. developing fungal biofilms strains, underlining their possible & beneficial use as an antifungal & hostile to biofilm affecting compounds, perhaps, elective compounds usage for antifungal in clinical treatments & the food processing business, however, these can be utilized to stop or retard the growth & development of fungal biofilms responsible for infection & waste of food materials [51]. Table 3 shows the quercetin antibiofilm effect on bacteria.

Table 3. Quercetin's antibiofilm effect on bacteria.

S. No.	Biofilm-producing bacterial strains	C ₁₅ H ₁₄ O ₉ (quercetin) or it is analog/ conjugates	The effective activity of Quercetin
1	<i>Streptococcus pneumonia</i>	quercetin (C ₁₅ H ₁₄ O ₉)	Quercetin analog reduced the Biofilm formation [52].

	strain D39		
2	Clinical separation of <i>P. Aeruginosa</i> strain	quercetin (C ₁₅ H ₁₄ O ₉)	Inhibition of the Biofilm formation and twitch movements [53].
3	MSSA- ATCC (29213), MRSA- ATCC (33591), & clinical separation of <i>S. aureus</i>	quercetin (C ₁₅ H ₁₄ O ₉)	Inhibits 50% of biofilm formation [54].
4	<i>S. aureus</i> (ATCC)-6538	quercetin (C ₁₅ H ₁₄ O ₉)	It has not just nullified the bacterial biofilm frame & <i>S. aureus</i> as well as also Inhibition of adhesion outflow, & genes which regulate the virus [55].
5	A clinical separation of <i>S. aureus</i>	C ₁₅ H ₁₄ O ₉ -AgNP analogue	(Quercetin-AgNP) modified analog directly diminished the development of bacterial biofilms [56].

Antiallergic activity:

The anti-allergic activity of quercetin, which inhibits the enzymes & inflammation/allergic mediators, had been widely investigated. It has truly known that quercetin inhibits mast cell activation through inhibition of Ca²⁺ entry inside the cell, histamine, leukotrienes, & prostaglandins synthesis & its liberation in the local tissues. Quercetin also has anti-allergic properties by inhibiting enzymes and inflammasomes [57].

At concentrations of 3–30 micromole, quercetin stops/blocks the release & synthesis of histamine and proinflammatory/proallergic mediators including {Tumour-Necrosis-Factor- α (TNF- α)}, {Interleukin (IL)-1, IL-6, and IL-8}, as well as (entry of calcium inside the cell) & (protein- kinase Cs signaling). Quercetin with Glucosyl conjugation is a useful technique for increasing bioavailability [58].

Recently, Sato, Surojanametakul *et al.* reported the antiallergic effects of around 46 vegetables, in which the onion was known as a more effective anti-allergic vegetable. The identification of onion assortments with more anti-allergic movement can lead to the advancement & creation of various assortments to give benefits to keep our body healthy [59]. Inhibition of Hindrance of passive cutis anaphylaxis outcomes is generally utilized in the model of *in vivo* to screening in the antiallergic composites [60].

Antiproliferative activity:

G Scambia *et al.* reported that quercetin has better effectiveness in the ovary cancer cell. Also, a study shows a good antiproliferative effect during *in vitro* study with cisplatin in the carcinoma cells of rats [61]. An investigation shows the ratio report between apple intakers having prostate or

breast cancer. The report was found a strong effect of antioxidants & antiproliferative through *in vivo* and *in vitro* study. The higher effect shows on cell development when combinational drugs are used having a particular ratio of dose [61, 62]. Chemotherapy results are not satisfactory in the treatment of breast cancer. So alteration in chemotherapy may increase effectiveness and decrease toxicity by inducing a rich diet of fruits and vegetables [62].

Mauro Piantelli *et al.* reported the presence of type 2 estrogen binding site in meningiomas of humans and the antiproliferative activity of quercetin to treat this tumor [63]. Full clarification of quercetin's antiproliferative effect mechanism has not been justified [63, 67]. The combination of quercetin and glucose dismiss the antiproliferative impacts of the aglycone. The counter proliferative impact of some combined metabolites from catechin & quercetin was concentrated in three malignancy cell lines and contrasted with the impacts of their unconjugated structures [64].

Quercetin & epigallocatechin gallate shows the antiproliferative effect and provokes apoptosis in the prostate cancerous cell. Through the hindrance of the catechol-O-methyl transferase, the development of less dynamic methyl metabolites might be decreased & the anticancer strength of green tea polyphenols & quercetin might be improved [65]. To treat the tumors by chemotherapy, quercetin & cis-diamminedichloroplatinum are suggested because quercetin helps to enhance the antitumor or antiproliferative activity of cis-DDP [66].

Conclusion: It is concluded from the manuscript that quercetin has various roles in the treatment of diseases. It shows various pharmacological activities with great efficacy. The manuscript mainly describes the antioxidant, anticancer, antibacterial and antimicrobial, anti-inflammatory, antidiabetic, antihypertensive, antifungal, anti-allergic and antiproliferative properties of the quercetin. It also describes the extraction of quercetin and the sources from which this is obtained. From the manuscript, it is concluded that it is generally obtained from the plant so it is cheap and easily available and due to its herbal nature it is easily utilized by the majority of people.

Reference:

- [1] Erkoç, Ş.; Erkoç, F.; Keskin, N. Theoretical investigation of quercetin and its radical isomers. *J. Mol. Struct.*, **2003**, *631*(1-3), 141-146.
- [2] Pool, H.; Mendoza, S.; Xiao, H.; McClements, D.J. Encapsulation and release of hydrophobic bioactive components in nanoemulsion-based delivery systems: impact of physical form on quercetin bioaccessibility. *Food Funct.*, **2013**, *4*(1), 162-174.
- [3] Mouffok, S.; Haba, H.; Lavaud, C.; Long, C.; Benkhaled, M. Chemical constituents of *Centaurea omphalotricha* Coss. & Durieu ex Batt. & Trab. *Rec. Nat. Prod.*, **2012**, *6*(3), 292-5.
- [4] Smith, A.J.; Kavuru, P.; Wojtas, L.; Zaworotko, M.J.; Shytle, R.D. Cocrystals of quercetin with improved solubility and oral bioavailability. *Mol. Pharm.*, **2011**, *8*(5), 1867-1876.

- [5] Chafer, A.; Fornari, T.; Berna, A.; Stateva, R.P. Solubility of quercetin in supercritical CO₂+ ethanol as a modifier: measurements and thermodynamic modelling. *J. Supercrit. Fluids*, **2004**, 32(1-3), 89-96.
- [6] Batiha, G.E.S.; Beshbishy, A.M.; Ikram, M.; Mulla, Z.S.; El-Hack, M.E.A.; Taha, A.E.; Algammal, A.M.; Elewa, Y.H.A. The pharmacological activity, biochemical properties, and pharmacokinetics of the major natural polyphenolic flavonoid: quercetin. *Foods*, **2020**, 9(3), 1-16.
- [7] Alrawaiq, N.S.; Abdullah, A. A review of flavonoid quercetin: metabolism, bioactivity and antioxidant properties. *Int. J. PharmTech Res.*, **2014**, 6(3), 933-941.
- [8] Li, Y.; Yao, J.; Han, C.; Yang, J.; Chaudhry, M.T.; Wang, S.; Liu, H.; Yin, Y. Quercetin, inflammation and immunity. *Nutrients*, **2016**, 8(3), 1-14.
- [9] Mendoza, L., Yañez, K.; Vivanco, M.; Melo, R.; Cotoras, M. Characterization of extracts from winery by-products with antifungal activity against *Botrytis cinerea*. *Ind. Crop and Prod.*, **2013**, 43, 360-364.
- [10] Iacopetta, D.; Grande, F.; Caruso, A.; Mordocco, R.A.; Plutino, M.R.; Scrivano, L.; Ceramella, J.; Muià, N.; Saturnino, C.; Puoci, F.; Rosano, C. New insights for the use of quercetin analogs in cancer treatment. *Future Med. Chem.*, **2017**, 9(17), 2011-2028.
- [11] Xu, D.; Hu, M.J.; Wang, Y.Q.; Cui, Y.L. Antioxidant activities of quercetin and its complexes for medicinal application. *Molecules*, **2019**, 24(6), 1-15.
- [12] Andres, S.; Pevny, S.; Ziegenhagen, R.; Bakhiya, N.; Schäfer, B.; Hirsch-Ernst, K.I.; Lampen, A. Safety aspects of the use of quercetin as a dietary supplement. *Mol. Nutr. Food Res.*, **2018**, 62(1), 1-15.
- [13] Sun, D.; Li, N.; Zhang, W.; Zhao, Z.; Mou, Z.; Huang, D.; Liu, J.; Wang, W. Design of PLGA-functionalized quercetin nanoparticles for potential use in Alzheimer's disease. *Colloids Surf. B Biointerfaces*, **2016**, 148, 116-129.
- [14] Ferreira, P.E.B.; Lopes, C.R.P.; Alves, A.M.P.; Alves, É.P.B.; Linden, D.R.; Zanoni, J.N.; Buttow, N.C. Diabetic neuropathy: an evaluation of the use of quercetin in the cecum of rats. *World J. Gastroenterol.*, **2013**, 19(38), 6416-6426.
- [15] Olson, E.R.; Melton, T.; Dickinson, S.E.; Dong, Z.; Alberts, D.S.; Bowden, G.T. Quercetin potentiates UVB-Induced c-Fos expression: implications for its use as a chemopreventive agent. *Cancer Prev. Res.*, **2010**, 3(7), 876-884.
- [16] Dajas, F. Life or death: Neuroprotective and anticancer effects of quercetin. *J. Ethnopharmacol.*, **2012**, 143(2), 383-396.

- [17] D'Andrea, G. Quercetin: a flavonol with multifaceted therapeutic applications?. *Fitoterapia*, **2015**, *106*, 256-271.
- [18] Lakhanpal, P.; Rai, D.K. Quercetin: a versatile flavonoid. *Internet J. Medical Update*, **2007**, *2*(2), 22-37.
- [19] Bischoff, S.C. Quercetin: potentials in the prevention and therapy of disease. *Curr. Opin. Clin. Nutr. Metab. Care*, **2008**, *11*(6), 733-740.
- [20] Brett, A.M.O.; Ghica, M.E. Electrochemical oxidation of quercetin. *Electroanalysis: An International Journal Devoted to Fundamental and Practical Aspects of Electroanalysis*, **2003**, *15*(22), 1745-1750.
- [21] Maalik, A.; Khan, F.A.; Mumtaz, A.; Mehmood, A.; Azhar, S.; Atif, M.; Karim, S.; Altaf, Y.; Tariq, I. Pharmacological applications of quercetin and its derivatives: a short review. *Trop. J. Pharm. Res.*, **2014**, *13*(9), 1561-1566.
- [22] Ishizawa, K.; Yoshizumi, M.; Kawai, Y.; Terao, J.; Kihira, Y.; Ikeda, Y.; Tomita, S.; Minakuchi, K.; Tsuchiya, K.; Tamaki, T. Pharmacology in health food: metabolism of quercetin in vivo and its protective effect against arteriosclerosis. *J. Pharmacol. Sci.*, **2011**, *115*(4), 466-470.
- [23] Olthof, M.R.; Hollman, P.C.; Vree, T.B.; Katan, M.B. Bioavailabilities of quercetin-3-glucoside and quercetin-4'-glucoside do not differ in humans. *J. Nutr.*, **2000**, *130*(5), 1200-1203.
- [24] Song, J.Y.; Yang, B.S. Quercetin shows the pharmacological activity to simultaneously downregulate the inflammatory and fibrotic responses to tissue injury in association with its ability to target multi-kinases. *Pharmacology*, **2018**, *102*, 142-153.
- [25] Nathiya, S.; Durga, M.; Devasena, T. Quercetin, encapsulated quercetin and its application—A review. *Analgesia*, **2014**, *10*(11), 20-26.
- [26] Wei, Y.Q.; Zhao, X.; Kariya, Y.; Fukata, H.; Teshigawara, K.; Uchida, A. Induction of apoptosis by quercetin: involvement of heat shock protein. *Cancer Res.*, **1994**, *54*(18), 4952-4957.
- [27] Kim, J.K.; Park, S.U. Quercetin and its role in biological functions: an updated review. *EXCLI journal*, **2018**, *17*, 856-863.
- [28] Wang, L.; Li, B.; Si, X.; Liu, X.; Deng, X.; Niu, X.; Jin, Y.; Wang, D.; Wang, J. Quercetin protects rats from catheter-related *Staphylococcus aureus* infections by inhibiting coagulase activity. *J. Cell. Mol. Med.*, **2019**, *23*(7), 4808-4818.
- [29] Granato, M.; Rizzello, C.; Montani, M.S.G.; Cuomo, L.; Vitillo, M.; Santarelli, R.; Gonnella, R.; D'Orazi, G.; Faggioni, A.; Cirone, M. Quercetin induces apoptosis and autophagy in primary effusion lymphoma cells by inhibiting PI3K/AKT/mTOR and STAT3 signaling pathways. *J. Nutr. Biochem.*, **2017**, *41*, 124-136.

- [30] Teekaraman, D.; Elayapillai, S.P.; Viswanathan, M.P.; Jagadeesan, A. Quercetin inhibits human metastatic ovarian cancer cell growth and modulates components of the intrinsic apoptotic pathway in PA-1 cell line. *Chem. Biol. Interact.*, **2019**, *300*, 91-100.
- [31] Seo, H.S.; Ku, J.M.; Choi, H.S.; Choi, Y.K.; Woo, J.K.; Kim, M.; Kim, I.; Na, C.H.; Hur, H.; Jang, B.H.; Shin, Y.C. Quercetin induces caspase-dependent extrinsic apoptosis through inhibition of signal transducer and activator of transcription 3 signaling in HER2-overexpressing BT-474 breast cancer cells. *Oncol. Rep.*, **2016**, *36*(1), 31-42.
- [32] Wang, Y.; Tao, B.; Wan, Y.; Sun, Y.; Wang, L.; Sun, J.; Li, C. Drug delivery based pharmacological enhancement and current insights of quercetin with therapeutic potential against oral diseases. *Biomed. Pharmacother.*, **2020**, *128*, 1-13.
- [33] Savic, I.M.; Nikolic, V.D.; Savic-Gajic, I.M.; Nikolic, L.B.; Moder, K.; Hopkins, M. Optimization of quercetin extraction from green tea (*Camellia sinensis*) using central composite design, and the pharmacological activity of the extract. *Chem. Biochem. Eng. Q.*, **2016**, *30*(1), 103-115.
- [34] Bjeldanes, L.F.; Chang, G.W. Mutagenic activity of quercetin and related compounds. *Science*, **1977**, *197*(4303), 577-578.
- [35] Yang, D.; Wang, T.; Long, M.; Li, P. Quercetin: Its Main Pharmacological Activity and Potential Application in Clinical Medicine. *Oxid. Med. Cell. Longev.*, **2020**, *2020*, 1-13.
- [36] Boots, A.W.; Li, H.; Schins, R.P.; Duffin, R.; Heemskerk, J.W.; Bast, A.; Haenen, G.R. The quercetin paradox. *Toxicol. Appl. Pharmacol.*, **2007**, *222*(1), 89-96.
- [37] de Boer, V.C.; Dihal, A.A.; van der Woude, H.; Arts, I.C.; Wolfram, S.; Alink, G.M.; Rietjens, I.M.; Keijer, J.; Hollman, P.C. Tissue distribution of quercetin in rats and pigs. *J. Nutr.*, **2005**, *135*(7), 1718-1725.
- [38] Vessal, M.; Hemmati, M.; Vasei, M. Antidiabetic effects of quercetin in streptozocin-induced diabetic rats. *Comp. Biochem. Physiol. C Toxicol. Pharmacol.*, **2003**, *135*(3), 357-364.
- [39] Ożarowski, M.; Mikołajczak, P.Ł.; Kujawski, R.; Wielgus, K.; Klejewski, A.; Wolski, H.; Seremak-Mrozikiewicz, A. Pharmacological effect of quercetin in hypertension and its potential application in pregnancy-induced hypertension: review of in vitro, in vivo, and clinical studies. *Evid. Based Complement. Alternat. Med.*, **2018**, *2018*, 1-20.
- [40] Formica, J.V.; Regelson, W. Review of the biology of quercetin and related bioflavonoids. *Food Chem. Toxicol.*, **1995**, *33*(12), 1061-1080.
- [41] Yamamoto, Y.; Oue, E. Antihypertensive effect of quercetin in rats fed with a high-fat high-sucrose diet. *Biosci. Biotech. Bioch.*, **2006**, *70*(4), 933-939.

- [42] Perez-Vizcaino, F.; Duarte, J.; Jimenez, R.; Santos-Buelga, C.; Osuna, A. Antihypertensive effects of the flavonoid quercetin. *Pharmacol. Rep.*, **2009**, *61*(1), 67-75.
- [43] Draganovic, D.; Lucic, N.; Jojic, D.; Milicevic, S. Correlation of oxidative stress markers with ultrasound and cardiocography parameters with hypertension induced pregnancy. *Acta Inform. Med.*, **2017**, *25*(1), 19-23.
- [44] Duarte, J.; Pérez-Palencia, R.; Vargas, F.; Angeles Ocete, M.; Pérez-Vizcaino, F.; Zarzuelo, A.; Tamargo, J. Antihypertensive effects of the flavonoid quercetin in spontaneously hypertensive rats. *Br. J. Pharmacol.*, **2001**, *133*(1), 117-124.
- [45] Mackraj, I.; Govender, T.; Ramesar, S. The antihypertensive effects of quercetin in a salt-sensitive model of hypertension. *J. Cardiovasc. Pharmacol.*, **2008**, *51*(3), 239-245.
- [46] Galindo, P.; Rodriguez-Gómez, I.; González-Manzano, S.; Dueñas, M.; Jiménez, R.; Menéndez, C.; Vargas, F.; Tamargo, J.; Santos-Buelga, C.; Pérez-Vizcaíno, F.; Duarte, J. Glucuronidated quercetin lowers blood pressure in spontaneously hypertensive rats via deconjugation. *PloS one*, **2012**, *7*(3), 1-8.
- [47] Tempesti, T.C.; Alvarez, M.G.; de Araújo, M.F.; Júnior, F.E.A.C.; de Carvalho, M.G.; Durantini, E.N. Antifungal activity of a novel quercetin derivative bearing a trifluoromethyl group on *Candida albicans*. *Med. Chem. Res.*, **2012**, *21*(9), 2217-2222.
- [48] Alves, C.T.; Ferreira, I.C.; Barros, L.; Silva, S.; Azeredo, J.; Henriques, M. Antifungal activity of phenolic compounds identified in flowers from North Eastern Portugal against *Candida* species. *Future Microbiol.*, **2014**, *9*(2), 39-146.
- [49] Gao, M.; Wang, H.; Zhu, L. Quercetin assists fluconazole to inhibit biofilm formations of fluconazole-resistant *Candida albicans* in in vitro and in vivo antifungal managements of vulvovaginal candidiasis. *Cell. Physiol. Biochem.*, **2016**, *40*(3-4), 727-742.
- [50] Oliveira, V.M.; Carraro, E.; Auler, M.E.; Khalil, N.M. Quercetin and rutin as potential agents antifungal against *Cryptococcus* spp. *Braz. J. Biol.*, **2016**, *76*(4), 1029-1034.
- [51] Rocha, M.F.G.; Sales, J.A.; da Rocha, M.G.; Galdino, L.M.; de Aguiar, L.; Pereira-Neto, W.D.A.; de Aguiar Cordeiro, R.; Castelo-Branco, D.D.S.C.M.; Sidrim, J.J.C.; Brilhante, R.S.N. Antifungal effects of the flavonoids kaempferol and quercetin: a possible alternative for the control of fungal biofilms. *Biofouling*, **2019**, *35*(3), 320-328.
- [52] Wang, J.; Song, M.; Pan, J.; Shen, X.; Liu, W.; Zhang, X.; Li, H.; Deng, X. Quercetin impairs *Streptococcus pneumoniae* biofilm formation by inhibiting sortase A activity. *J. Cell. Mol. Med.*, **2018**, *22*(12), 6228-6237.

- [53] Vipin, C.; Mujeeburahiman, M.; Ashwini, P.; Arun, A.B.; Rekha, P.D. Anti-biofilm and cytoprotective activities of quercetin against *Pseudomonas aeruginosa* isolates. *Lett. Appl. Microbiol.*, 2019, 68(5), 464-471.
- [54] da Costa Júnior, S.D.; de Oliveira Santos, J.V.; de Almeida Campos, L.A.; Pereira, M.A.; Magalhães, N.S.S.; Cavalcanti, I.M.F. Antibacterial and antibiofilm activities of quercetin against clinical isolates of *Staphylococcus aureus* and *Staphylococcus saprophyticus* with resistance profile. *Int. J. Environ. Agric. Biotech.*, 2018, 3(5), 1948-1958.
- [55] Lee, J.H.; Park, J.H.; Cho, H.S.; Joo, S.W.; Cho, M.H.; Lee, J. Anti-biofilm activities of quercetin and tannic acid against *Staphylococcus aureus*. *Biofouling*, 2013, 29(5), 491-499.
- [56] Vanaraj, S.; Keerthana, B.B.; Preethi, K. Biosynthesis, characterization of silver nanoparticles using quercetin from *Clitoria ternatea* L to enhance toxicity against bacterial biofilm. *J. Inorg. Organomet. Polym. Mater.*, 2017, 27(5), 1412-1422.
- [57] Mlcek, J.; Jurikova, T.; Skrovankova, S.; Sochor, J. Quercetin and its anti-allergic immune response. *Molecules*, 2016, 21(5), 1-15.
- [58] Makino, T.; Kanemaru, M.; Okuyama, S.; Shimizu, R.; Tanaka, H.; Mizukami, H. Anti-allergic effects of enzymatically modified isoquercitrin (α -oligoglucosyl quercetin 3-O-glucoside), quercetin 3-O-glucoside, α -oligoglucosyl rutin, and quercetin, when administered orally to mice. *J. Nat.l Med.*, 2013, 67(4), 881-886.
- [59] Sato, A.; Zhang, T.; Yonekura, L.; Tamura, H. Antiallergic activities of eleven onions (*Allium cepa*) were attributed to quercetin 4'-glucoside using QuEChERS method and Pearson's correlation coefficient. *J. Funct. Foods.*, 2015, 14, 581-589.
- [60] Escribano-Ferrer, E.; Queralt Regué, J.; Garcia-Sala, X.; Boix Montañés, A.; Lamuela-Raventos, R.M. In vivo anti-inflammatory and antiallergic activity of pure naringenin, naringenin chalcone, and quercetin in mice. *J. Nat. Prod.*, 2019, 82(2), 177-182.
- [61] Scambia, G.; Ranelletti, F.O.; Bonanno, G.; De Vincenzo, R.; Piantelli, M.; Mancuso, S. Synergistic antiproliferative activity of quercetin and cisplatin on ovarian cancer cell growth. *Anti-cancer Drugs*, 1990, 1(1), 45-48.
- [62] Yang, J.; Liu, R.H. Synergistic effect of apple extracts and quercetin 3- β -D-glucoside combination on antiproliferative activity in MCF-7 human breast cancer cells in vitro. *J. Agric. Food Chem*, 2009, 57(18), 8581-8586.
- [63] Piantelli, M.; Rinelli, A.; Maorì, E.; Maggiano, N.; Larocca, L.M.; Capelli, A.; Scerrati, M.; Roselli, R.; Iacoangeli, M.; Scambia, G.; Ranelletti, F.O. Type II estrogen binding sites and antiproliferative activity of quercetin in human meningiomas. *Cancer*, 1993, 71(1), 193-198.

[64] Delgado, L.; Fernandes, I.; González-Manzano, S.; de Freitas, V.; Mateus, N.; Santos-Buelga, C. Anti-proliferative effects of quercetin and catechin metabolites. *Food & Function*, **2014**, 5(4), 797-803.

[65] Wang, P.; Heber, D.; Henning, S.M. Quercetin increased the antiproliferative activity of green tea polyphenol (-)-epigallocatechin gallate in prostate cancer cells. *Nutr. Cancer*, **2012**, 64(4), 580-587.

[66] Hofmann, J.; Fiebig, H.H.; Winterhalter, B.R.; Berger, D.P.; Grunicke, H. Enhancement of the antiproliferative activity of cis-diamminedichloroplatinum (II) by quercetin. *Int. J. Cancer*, **1990**, 45(3), 536-539.

[67] Larocca, L.M.; Teofili, L.; Leone, G.; Sica, S.; Pierelli, L.; Menichella, G.; Scambia, G.; Panici, P.B.; Ricci, R.; Piantelli, M.; Ranelletti, F.O. Antiproliferative activity of quercetin on normal bone marrow and leukaemic progenitors. *Br. J. Haematol.*, **1991**, 79(4), 562-566.