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A NEW INSIGHTS AND PERSPECTIVE OF THERAPEUTIC POTENTIAL OF QUERCETIN

Leena Sahu[1], Harish Sharma[2] and Gyanesh Kumar Sahu*[1]

[1]Shri Shankracharya Technical Campus Shri Shankaracharya group of institutions, Faculty of Pharmaceutical Sciences, Junwani, Bhilai (C.G.).
[2]MJ College of Pharmacy, Junwani, Bhilai (C.G.).

***Corresponding Author: Gyanesh Kumar Sahu**
Assistant Professor Shri Shankracharya Technical Campus Shri Shankaracharya group of institutions, Faculty of Pharmaceutical Sciences, Junwani, Bhilai (C.G.).

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ABSTRACT
Quercetin is a natural flavonoid found in vegetables and fruits. There is growing evidence suggesting that quercetin has therapeutic potential for the prevention and treatment of different diseases, including cardiovascular disease, allergy, eye disease, cancer, and neurodegenerative disease. Quercetin is a bioavailability enhancer. Bioenhancer is an agent capable of enhancing bioavailability and bioefficacy of a particular drug with which it is combined, without any typical pharmacological activity of its own at the dose used Quercetin is a dietary antioxidant that prevents oxidation of low density lipoprotein in vitro. Phenolic hydroxyl groups at the B-ring and the 3-position are responsible for its free radical-scavenging activity. Quercetin also exerts a direct, pro-apoptotic effect in tumor cells, and can indeed block the growth of several human cancer cell lines at different phases of the cell cycle.

KEYWORDS: Quercetin, cancer, bioavailability.

INTRODUCTION

Herbal medicines

Herbal medicines are naturally occurring, plant-derived substances with minimal or no industrial processing that have been used to treat sickness within local or regional healing practices.[1] Herbal medicine is increasingly being validated by scientific investigation which seeks to understand the active chemistry of the plant. Many modern pharmaceuticals have been modeled on, or derived from chemicals found in plants. An example is the heart medication digoxin derived from foxglove (*Digitalis purpurea*).[2] Herbals have been used for health and medical purposes for several thousands of years, majority of people still using herbal medicine to meet their health needs. Medicinal plants are important sources for pharmaceutical manufacturing.[3]

Fig 1: Various type of herbal drug.

Bioenhancer

Bioenhancers are also called bioavailability enhancer. It is first time established in 1979 after the discovery of world's first bioenhancer Piperine. It is a pocket friendly drug technology which reduces the destruction, wastage and elimination of several orally administered drugs inside the body. A bioenhancer is an agent capable of enhancing bioavailability and bioefficacy of a particular drug with which it is combined, without any typical

pharmacological activity of its own at the dose used.[4] Or Bioenhancer are defined as substances that increase the bioavailability and bioefficacy of active substances with which they are combined without having any activity of their own at the dose used. Besides several classes of modern drugs like antibiotics, anti-cancer drugs, cardiovascular drugs, anti-inflammatory, central nervous drugs, etc., they also increase the bioavailability of vitamins and nutrients.[5] The term bioavailability is one of the principal pharmacokinetic properties of drugs. It shows the rate and extent of the active pharmaceutical ingredients in the blood. This helps in calculating that how much amount is absorbed from blood and how much is unabsorbed and first pass metabolized.[6] Bioavailability is the fraction of the dose administered that reaches the systemic circulation unchanged. The bioavailability term is used to encompass both the rate and extent of absorption from the site of administration to the systemic circulation.[7] These are also termed as 'absorption enhancers' which are functional excipients included in formulations to improve the absorption of a pharmacologically active drug.[8]

Bioenhancer should have novel property such as

- Nontoxic to humans or animals.
- It must be effective at very low concentration.
- Should be easy to formulate.
- Compatible with API and excipients.
- Most importantly, enhance uptake/absorption and activity of the drug molecules.[9]
- Should be unidirectional in action.
- Should be stable with time and environment.
- Should be easily formulated into a various dosage form.
- Should be easily available and cost effective.
- Should be rapid acting with predictable and reproducible activity.[10]

History of bioenhancer

The term 'bioavailability enhancer' was first coined by Indian scientists at the Regional Research Laboratory, Jammu (RRL, now known as Indian Institute of Integrative Medicine, Jammu), who discovered and scientifically validated piperine as the world's first bioavailability enhancer in 1979.[11] Bioenhancer is an ancient term of "Ayurveda" which implies the increase effect of drug in combination with it. Ayurveda terms it as "Yogvahi" in Sanskrit which indicates increase in effect by combination. In 1929, Bose has documented action of bioenhancer. He has used long paper to increase antihistaminic property of vasaka.[12] C.K. is the director of institute analyzed a list of formulation of ancient Indian Ayurveda and designed the occupied theory that Trikatu enhances efficacy of formulation.

Trikatu has three ingredients

1) Black pepper (Piper nigrum)
2) Long pepper (Piper longum)
3) Ginger (Zingiber officinale)[13]

Need of bioenhancer

To pass biological membrane molecules have to pass – solubility and molecular size. Molecules having poor lipid solubility and improper molecular size or both give poor absorption and poor bioavailability. Bioenhancers increases penetration through membranes and helps to solve problem of poor absorption and poor bioavailability.[14]

Bioavailability enhancement can be done by following

(A) Promoting the absorption of the drug from GIT.
(B) Inhibiting or reducing the rate of biotransformation of drugs in the liver or intestines.
(C) Modifying the immune system in such a way that the overall requirement of the drug is reduced substantially.
(D) Inhibiting the capability of pathogens or abnormal tissue to reject the drug, for example, efflux mechanisms frequently encountered with antimalarial, anticancer and antimicrobial drugs. Modifying the signaling process between host and pathogen ensuring increased accessibility of the drugs to the pathogens.
(E) Enhancing the binding of the drug with the target sites such as receptors, proteins, DNA, RNA, and the like in the pathogen, thus potentiating and prolonging its effect leading to enhanced antibiotic activity against pathogens.

Besides above mode of action, the bioenhancer agents may also be useful for promoting the transport of nutrients and the drugs across the blood brain barrier, which could be of immense help in the control of diseases like cerebral infections, epilepsy, and other CNS problems.[15]

Criteria of selection active ingredient

- Drugs adhered with poor bioavailability need higher dose to overcome the subtherapeutic range and exert its pharmacological effect because a large portion of dose gets consumed before it reached to target.
- For those drugs which have to be administer for a long period of time like in cancer or cardiovascular disease.
- Drugs having number of toxic effects and adhered to higher risk benefit ratio need to use this concept. Some time, to attain the MEC or MIC a high dose is used that also increase the fatal side effects on the other side.
- This has been seen in case of antianeoplastics, antiviral and multidrug resistance. Expensive drug molecules need to use cautiously because of very high cost of each milligram of drug.[16]

Concept of bioenhancer

The concept of bioenhancer is called Yogvahi in Ayurveda. Synergism that is, increase in the action of one molecule by another unrelated chemical is the hallmark of polyherbal formulation of Ayurveda. Specific Yogvahi or bioenhancer are termed as Anupaan

and sehpaan. Anupaan means food concomitantly given with the medicament to increase the effect of medicament, such as" Amrita Dhara" drops used for gastrointestinal diseases. Sehpaan means that the vehicle, which is during the manufacturing of the medicament, increases the effect of the medicament like for panchgavya ghrit and brahmi ghrit.[04]

Classification of bioenhancer

Bioenhancer can be classified based on:-

1. There origin
2. Mechanism of action

Classification on the basis of plant origin

Plant origin	Animal origin
Piperine ,curcumin , carum carvi , stevia, ginger, allicin, aloevera, geinstein, capsaicin ,naringin, niagiridin, liquirice ,lysergol,cuminum cyminum.	Cow urine distillate

Fig 2 :- classification of bioenhancer

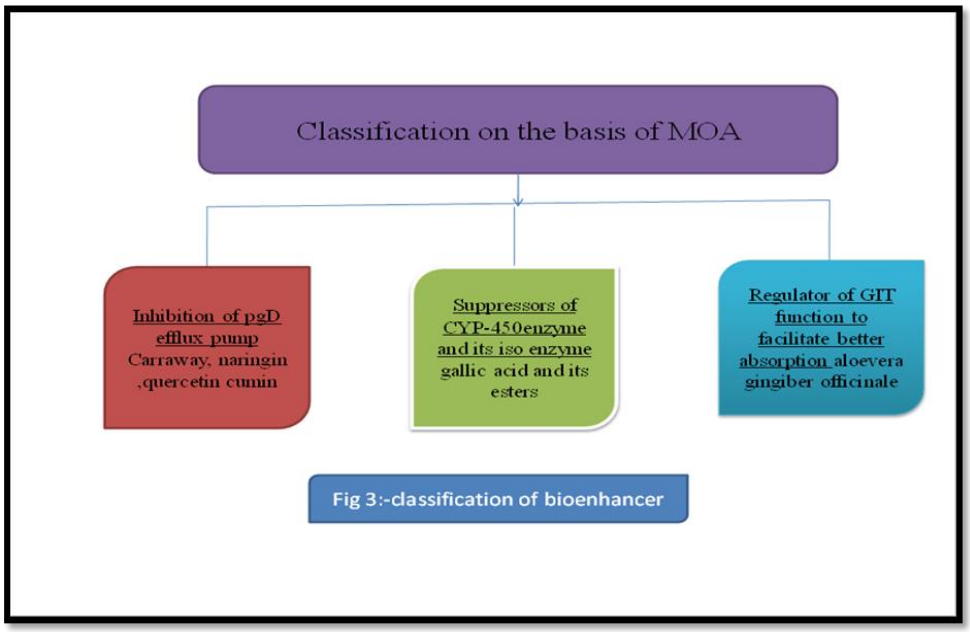

Fig 3:-classification of bioenhancer

Mechanism of action of bioenhancer

The following are the chief mechanisms via which the various bioenhancers exert their bioavailability enhancing properties on the drug molecules:

- By enhancing the absorption of orally administered drugs from gastrointestinal tract by increase in blood supply.
- By modulating the active transporters located in various locations eg. P-glycoprotein (P-gp) is an efflux pump which pumps out drugs and prevent it from reaching the target site. Bioenhancers in such case act by inhibiting the P-gp.
- Decreasing the elimination process thereby extending the sojourn of drug in the body.[17]
- It inhibits or reduces the rate of biotransformation of drug in liver or intestine.
- By modifying immune system to reduce overall requirement of drug.
- By allowing entry into pathogen or by increasing penetration where they become persistors within macrophages such as for mycobacterium tuberculosis example: nitrile glycosides.
- By inhibiting ability of pathogen or tissue to reject the dru.[18]
- By stimulating gamma glutamyl transpeptidase (GGT) actively which enhance amino acid uptake. By modifying signaling process between host and pathogen to increase accessibility of drug to pathogen.
- By enhancing binding of drug to receptors, proteins, DNA, RNA and potentiate and prolong its effect. Cholagogous affect i. e. it stimulate gall bladder contraction to promote flow.[19]

Hurdles with bioenhancer

Although bio-enhancers in drug delivery have been successful, not all approaches have met with the same success. New bio-enhancers being developed come with challenges which have to be surmounted. One of the challenges is to improve on properties of drug formulations such as long circulation in the blood, increased functional surface area, protection of incorporated drug from degradation, crossing of biological barriers and site-specific targeting.[20] Another

challenge of research and development of herbal bioenhancers is large scale production. There is always a need to scale up laboratory or pilot technologies for eventual commercialization. The challenges of scaling up include low concentration of nonmaterial's, agglomeration and the chemistry process; it is easier to modify nonmaterial's at laboratory scale for improved performance than at large scale. Advances in herbal bio-enhancers also provide new challenges for regulatory control. There is an increasing need to have regulations that would account for physicochemical and pharmacokinetic properties of nano drug products, which are different from conventional drug products.[21] Bioenhancers propose a newer concept in the discovery based on traditional system of Indian medicine. The improvements in this concept will definitely lead to reduction in cost of drug, toxicity and other adverse effects and will have a beneficial influence on the economy of the country. It is safe, effective, economical, easily procured too.

Thus, the approach of bioenhancer in modern medicine is very essential today and the development of bioenhancers from other sources has become the need of the hour.[22]

Drug absorption barrier

The drug must cross the epithelial barrier of the intestinal mucosa for its transportation from the lumen of the gut into the systemic circulation and exert its biological actions. There are many anatomical and biological barriers for the oral drug delivery system to penetrate the epithelial membrane. There are many structures in the intestinal epithelium which act as barriers to the transfer of drugs from the gastrointestinal track to the systemic circulation. The membranes around cells are lipid bilayers containing proteins such as receptors and carrier molecules.[23] The drug molecules larger than about 0.4 nm have difficulty in passing through these aqueous channels.[24] Recent work has shown that drug efflux pumps like P-glycoprotein possess a very important role in inhibiting efficient drug entry into the systemic circulation.[25] P-gp is a type of ATPase and an energy dependent transmembrane drug efflux pump it belongs to members of ABC transporters. It has a molecular weight of -170 kDa and has 1280 amino acid residues. A lot of bioenhancers works by inhibiting this efflux pump.[26]

Method used for enhancement of absorption of orally administered drug

1. **Absorption enhancer:** - Many of the absorption enhancers are effective in improving the intestinal absorption, such as bile salts, surfactants, fatty acids, chelating agents, salicylates and polymers. Chitosan, particularly trimethylated chitosan, increases the drug absorption via paracellular route by redistribution of the cytoskeletal F-actin, causing the opening of the tight junctions. Bile, bile salts and fatty acids are surfactants which act as absorption enhancers by increasing the solubility of hydrophobic drugs in the aqueous layer or by increasing the fluidity of the apical and basolateral membranes. Calcium chelator such as EGTA and EDTA enhances absorption by reducing the extracellular calcium concentration, leading to the disruption of cell-cell contacts.[27]
2. **Prodrug:** - Various ampicillin derivatives are the well-known examples of increasing the lipophilicity of agents, to enhance absorption of a polar drug by the strategy of prodrug. Ampicillin because of its hydrophilic nature is only 30% - 40% absorbed from the gastrointestinal tract. By esterification of carboxyl group of ampicillin, the produgs of ampicillin such as pivampicillin, bacampicilln and talampicillin were synthesized.[28]
3. **Dosage form and other pharmaceutical approaches:-** Utilization of permeability-enhancing dosage forms is one of the most practical approaches to improve the intestinal absorption of poorly absorbed drugs. Various dosage formulations such as liposome's and emulsions enhanced the intestinal absorption of insoluble drugs.[29] Particle size reduction methods such as micronization, nanoparticular carriers, and complexation and liquid crystalline phases also maximize drug absorption.[30]
4. **P glycoprotein inhibitors:** - P-glycoprotein inhibitors reverse P – glycoprotein - mediated efflux in an attempt to improve the efficiency of drug transport across the epithelial membrane. P - glycoprotein inhibitors influence the metabolism, absorption, distribution, and elimination of P - glycoprotein substrates in the process of modulating pharmacokinetics.[31]

Novel drug delivery system

Novel Drug delivery System (NDDS) refers to the approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effects. NDDS is a system for delivery of drug other than conventional drug delivery system.[32]

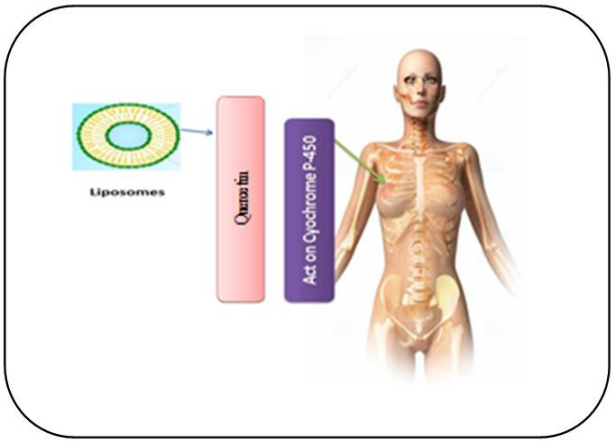

Fig. 4: Quercetin liposome act on the lung cancer.

Quercetin

Quercetin, a flavonoid obtained in fruits and vegetables, has unique biological properties that may improve mental/physical performance and reduce infection risk.[33] The name quercetin (3,3',4',5,7-pentahydroxyflavone) comes from the Latin word "Quercetum" which means Oak Forest, belongs to the class called flavonols that cannot be produced in the human body .It is one of the most abundant dietary flavonoid found in fruit(mainly citrus) green leaf vegetable as well as seed buckwheat, nuts, flowers, bark, broccoli, olive oil, apples, onion, green, tea, red, grapes, red wines, dark cherries and berries such as blue berries and cranberries. The highest concentration of flavonols found in vegetables such as onion and broccoli fruit such as apple cherries and berries and drinks such as tea and red wine.[34]

Plant name	family	geographical distribution	traditional use
Morus alba	Moraceae	China	Diet
Centella asiatica	Apiaceae	India	Wound healing
Camellia cinensis	Theaceae	southeast Asia	analgesic, antiviral, antidiabetic, Bronchodilator
Nasturtium officinale	Brassicaceae	Globally distributed	Reduce risk of cancer
Brassica olracea var. Italica (broccoli)	Brassicaceae	Europe and Asia	prevent fluid retention and cancer
Asparagus officinale	Asparagaceae	Egypt, Europe, China, mexico	antiulcer, antitussive antineoplastic
Hypericum hircimum	Clusiaceae	Britain	Antioxidant
Malus domestica	rosaceae	north america	decrease the risk of cardiovascular disease and cancer

Fig 5: List of some quercetin containing plant.

Pharmacological importance of quercetin

1. Antioxidant property

Quercetin is considered to be a strong antioxidant due to its ability to scavenge free radicals and bind transition metal ions. These properties of quercetin allow it to inhibit lipid peroxidation.[35]

Lipid peroxidation is the process by which unsaturated fatty acids are converted to free radicals via the abstraction of hydrogen.[36] The subsequent free radicals are oxidized by molecular oxygen to create lipid peroxy radicals. This process is propagated by the resulting lipid peroxy radicals extracting hydrogen from other unsaturated fatty acid molecules to create more free radicals. It is catalyzed, in part, by the presence of trace amounts of transition metal ions. Lipid peroxidation can create deleterious effects throughout the body, such as cardiovascular and neurodegenerative diseases; however, it can be terminated by antioxidants, like quercetin, which interfere by reacting with the radicals formed.[37]

Mechanism of action

- **Antioxidative action:-** Living organisms have developed antioxidant line of defense systems include enzymatic and non-enzymatic antioxidants that keep in check ROS/RNS level and repair oxidative cellular damage. The major enzymes, constituting the first line of defense, directly involved in the neutralization of ROS/RNS are: superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx). The second line of defense is represented by radical scavenging antioxidants such as vitamin C, vitamin A and plant phytochemicals including quercetin that inhibit the oxidation chain initiation and prevent chain propagation .This may also include the termination of a chain by the reaction of two radicals.[38]
- **Direct radical scavenging action:-** Quercetin acting as free radical scavengers was shown to exert a protective effect in reperfusion ischemic tissue damage. Quercetin prevents free radical induced tissue injury by various ways. One way is the direct scavenging of free radicals. By scavenging free radicals, Flavonoid; particularly Quercetin can inhibit LDL oxidation in vitro. This action protects against atherosclerosis.[39]

2. Antiviral activity:- Quercetin has shown antiviral activity towards a wide range of viruses. For instance, quercetin has been documented for its efficacy against the human T-lymphotropic virus 1, as well as the Japanese encephalitis virus (JEV)

caused by Japanese encephalitis, the mosquito-borne disease. Furthermore, quercetin has been reported to suppress the dengue virus type-2 and hepatitis C virus by suppressing the nonstructural protein 3 protease activity.[40] Other Quercetin formulations, such as quercetin-3-O-β-D-glucuronide, quercetin-enriched lecithin formulations, and quercetin 7-rhamnoside have been reported for their efficacy against the porcine epidemic diarrhea virus and influenza-A virus.[41] Although the etiology of cancer may be multifactorial (e.g. diet, genetic, environment), there is wide recognition that reactive oxygen and nitrogen species (ROS/RNS) play a pivotal role in the pathophysiological process. ROS/RON have been shown to be carcinogenic and may exert their deleterious effects by causing DNA damage, alter cell signaling pathways (MAPK, NFkB, AP-1, PLA, ASK-1) and modulate gene expression (proto-oncogene, tumour suppressor gene). In various animal and test tube studies, quercetin has been shown to inhibit the growth of cancer cells including those from breast, colon, prostate and lung cancers63. Quercetin by virtue of its anti-oxidant property prevents reactive oxygen species induced DNA damage, leading to mutational changes.[42]

3. **Anti-inflammatory effect:** Quercetin might help reduce inflammation. One study on animals found that quercetin prevented both acute and chronic inflammation, in addition to showing anti-arthritis properties. Results from human studies have provided mixed results, however. While research on healthy male athletes found that quercetin could reduce inflammation, it did not have the same effect in women with arthritis.[43] Quercetin was reported as a long lasting anti-inflammatory substance that possesses strong anti-inflammatory capacities. It possesses anti-inflammatory potential that can be expressed on different cell types, both in animal and human models. It is known to possess both mast cell stabilizing and gastrointestinal cytoprotective activity. It can also play a modulating, biphasic and regulatory action on inflammation and immunity. Additionally, quercetin has an immunosuppressive effect on dendritic cells function.[44]
4. **Peptic ulcer:** Quercetin seems to play a very important role in the prevention and treatment of peptic ulcer. It acts by promoting mucus secretion, thereby serves as gastroprotective agent. Apparently, many peptic ulcers can be caused by infectious bacteria, known as Helicobacter pylori. Quercetin has been shown to inhibit the growth of this bacterium in in-vitro studies.[45]
5. **Diabetic complications:** Quercetin has been found to be an inhibitor of the enzyme aldose reductase, which plays a role in converting glucose (sugar) to sorbitol (a sugar alcohol) in the body. People with diabetes develop secondary problems, such as neuropathy, retinopathy, diabetic cataracts, and nephropathy because of sorbitol buildup in the body. Quercetin may therefore be beneficial in the nutritional management of diabetes, but clinical studies need to be conducted to verify these effects, which have been observed in nonhuman experiments.[46]
6. **Gout:** Quercetin by virtue of its xanthine oxidase inhibitory nature prevents the production of uric acid, thereby easing the gout symptom.[42]
7. **Neurological effects:-** Quercetin is neuroprotective as well as neurotoxic. Therefore, it has been reported to behave as a neuroprotector in rat brain when used in combination to fish oil. Quercetin has been reported to show beneficial effects against neurodegenerative diseases (example, Alzheimer's disease) where it shows inhibitory effect against acetylcholinesterase.[47] Moreover, quercetin has been reported to reduce the oxidative stress induced by 6- hydroxydopamine in neurons from the brain striatum of rats. A study on healthy P19 neurons reported that quercetin treatment did not affect neuron survival but depletion in intracellular glutathione contents has been observed which can affect working of nervous system.[48]
8. **Antimycobacterial potential of quercetin and rutin:** The minimum inhibitory concentration (MIC) of quercetin and rutin were determined using MABA on a drug sensitive strain of M. tuberculosis H37Rv and was found to be 6.25µg/ml and 25µg/ml respectively. The standard drugs PZA, CIP and STM were used as positive control. Quercetin was found very potent and showed significant inhibition compared to rutin (quercetin-3-O-rutinoside). M. tuberculosis is a slow-growing intracellular pathogen which has a complex cell envelope containing mycolic acids and a diversity of other lipids, many of which are unique for mycobacteria. The evaluation of anti-TB potential of flavonoids using 96-well microplate alamar blue assay offers the advantages of less sample requirements and low cost.[49]

Table 1: Amount of Quercetin in selected food:[50]

Food	Quercetin/100gm	Myricetin mg/100gm	Kaempferol mg/100gm
Broccoli raw	2.8	0.0	6.3
Carrots, Raw	0.4	0.0	0.0
Celery, Raw	3.5	-	-
Cocoa powder, unsweetened	20.1	-	-
Cranberries, Raw	14.0	4.3	0.1
Onion, Raw	22.6	0.0	0.3

Extraction method of quercetin

1. **Conventional solvent extraction:-** As the solvent, certain concentration of ethanol solution was applied solely. Because the yield of quercetin and its glycoside using 60% ethanol was 5 times higher than that using pure distilled water, meanwhile, there is no significant difference from the case of methanol. Hence, there were 3 control factors subjected as the variables of CSE; the concentration of ethanol solution, the process time, and the temperature of extraction.[51] A sample of powdered OSW (exactly 0.5 g) was mixed in a glass vial with 30 mL of the extraction solvent (59% ethanol, pH 2). The mixture was stirred on a heated magnetic stirrer for 35 min at 49 °C, with the temperature monitored using a thermometer. After extraction, the vial was immediately cooled by chilled water. The extract was filtered through a 0.45-lm PVDF membrane syringe filter before injection into the HPLC system.[52]
2. **Microwave assisted extraction: -** MAE experiments were performed with a MSP-100E multimode microwave extraction system (maximal power: 850W, Beijing Rayme Sci. and Tech. Institute, Beijing, China). The MSP-100E instrument has an internal temperature control system with a fiber temperature probe and a pressure control system, which respectively monitors the temperature and the pressure inside the vessel. In all of the experiments, the pressure was set under 300 kPa to prevent the dissolution of the target compound. A 20 ml ethanol solution was added to 0.5 g of dried sample powders placed in an inner vessel. The extraction was carried out with different extraction conditions. Extraction solutions were filtered through a 0.45 µm filter prior to chromatographic analysis.[53] Recently, advanced techniques have become available to reduce the loss of bioactive compound without increasing the extraction time. Therefore, microwave-assisted extraction is demonstrated to be a good technique in multiple fields, especially in the medicinal plant area. Moreover, this technique reduced the losses of the biochemical compounds being extracted. Microwave-assisted extraction (MAE) has been used as an alternative to conventional techniques for the extraction of antioxidants because of its ability to reduce both time and extraction solvent volume.[54]
3. **Ultrasound assisted technique:-** Ultrasound-assisted extraction (UAE) was carried out in an ultrasonic bath (power 100 W). One gram of dried powder was placed in a beaker with 40 ml of 70% ethanol solution. The beaker was immersed in the ultrasonic bath and extracted for 30 min. The sample was filtered through a 0.45 µm filter prior to chromatographic analysis.[55] Ultrasound-assisted extraction (UAE) has been used in diverse applications of food-processing technology to extract bioactive compounds from plant materials. Ultrasound, with levels greater than 20 kHz, is used to disrupt plant cell walls, which helps improve the solvent's ability to penetrate the cells and obtain a higher extraction yield.[56] Extraction of phenolic compounds by ultrasound has grown during recent years due to its role in reducing the amount of solvent and energy used. Corrales et al. have shown that UAE can break down plant tissue and work properly during the production process and release of active compounds in solvents with a high efficiency.[57]

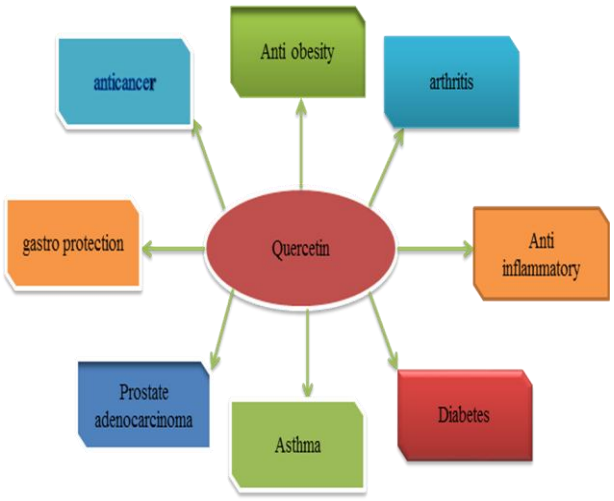

Fig. 6: Different application of quercetin.

Table 2: Quercetin based herbal formulation.

S. no.	Active ingredient	Formulation	Method of preparation	Route of administration	References
1.	Quercetin	Quercetin liposome	Reverse evaporation	intranasal	[58]
2.	Quercetin	Quercetin microspheres	Solvent evaporation	In vitro	[59]
3.	Quercetin	Quercetin floating microsphere	Emulsion solvent evaporation method	oral	[60]
4	Quercetin	Quercetin lipid based system	Quercetin phospholipid complexation	oral	[61]
5.	Quercetin	Quercetin phytosome	Thin layer hydration method	Orally	[62]
6.	Quercetin	Quercetin paclitaxol nanoparticle	ionic cross linking method	In vitro	[63]
7.	Quercetin	Quercetin loaded micro emulsion	-	Topical	[64]

Table 3: Patent on quercetin herbal controlled formulation.

Patent no.	Active ingredient	Novel system incorporation	references
Us patent 7569236132	Flavonoid (such as quercetin) and terpenes (ginkgolipid A,B, C and J)	microgranules	[65]

Recent Advances

Onset of the polymeric formulation approach in quercetin delivery, with its biodegradability, better loading efficiency, non-toxicity, prominent focus has been on generating improved bioavailability of the drug to exert desired effects in the body.[66] In 2014, Caddeo et al. proposed preparation and utilization of chitosan/xanthan gum microparticles to elevate the oral bioavailability of quercetin by optimizing the release in the colon. Multiparticulate tablet of liposomes and chitosan–xanthan gum complex were able to bypass the stomach and successfully delivered anti-inflammatory phycocyanin to the colon following oral administration. The spray-dried system exhibit good drug retention until it reached the colon.[67] The prepared microparticles showed significant quercetin loading with approximately 5 mm size and almost smooth spherical structure. In order to prevent acidic degradation in the stomach and to ensure controlled release in the colon quercetin loaded microparticles were compressed into tables and further coated with Eudragit®. The tablets showed pH responsive release of quercetin in the colonic environment following non-Fickian mechanism of release. Therefore chitosan/xanthan gum microparticles compressed tables could be a promising oral dosage form for successful quercetin delivery to the colon in treating diabetes and its related health problems.[68] Zhang et al.investigated quercetin-loaded chitosan nanoparticles were prepared by the ionic gelation of cationic chitosan with tripolyphosphate (TPP) anions to enhance oral bioavailability of the flavonoid. Moreover antioxidant activity of quercetin loaded particles also indicated that chitosan nanoparticles were useful in improving quercetin oral bioavailability. Again another report showed utilization of chitosan–lecithin nanoparticles for topical administration of quercetin increasing its bioactivity for treatment of several skin related problems like cutaneous oxidative stress and inflammation etc.[69]

Another important study was conducted by Tan et al. in for delivering quercetin perorally using nanomicelles, prepared from diblock copolymer of polyethylene glycol (PEG)-derivatized phosphatidylethanolamine (PE). The size of the nanomicelles varied between 15.4 to 18.5 nm, with significant incorporation (~88.9%) of quercetin. The study nanomicelles were specially developed for oral anti-cancer treatment, but these formulations could also be employed as potential delivery system of quercetin for anti-diabetic treatment.[66] A biocompatible quercetin loaded magnetic core–shell nanoparticle-based system (surface coating of Fe3O4 magnetic nanoparticles with a polymer poly (lactic-co-glycolic acid) (PLGA) for successful targeting lung cancer cells via nebulization.[70]

Future prospect

Taking leads from ayurveda and other traditional ways of medicine is nothing new for a modern researcher. Origin of about 75% of antimicrobial and 60% of anticancer drugs approved for clinical use from 1981 to 2002 could be traced back to nature.[71] Various cohort studies indicated an inverse association between Flavonoids intake (Quercetin) and coronary heart disease mortality. These studies are promising and indicate that flavonoids may be useful food compounds. Flavonoids have received much attention in the literature over the past 10 years and a variety of potential beneficial effects have been elucidated. However, most of the studies have been conducted in vitro studies; therefore, it is difficult to draw definite conclusion about the usefulness of flavonoids in the diet. Furthermore, insufficient methods are available to measure oxidative damage in vivo and the measurement of objective endpoints remains difficult.[72] Although recently some studies have been conducted on absorption and excretion of flavonols including quercetin but there is a need to improve analytic techniques to allow collection of more data in this aspect. Data on the long-term consequences of chronic quercetin ingestion are especially scarce. To conclude, in vivo studies could be performed to give a hopeful picture for the future. Currently, the intake of fruit, vegetables, and beverages (e.g., tea and moderate amounts of red wine) containing quercetin is recommended, although it is too early to make recommendations on daily quercetin intakes.[73]

CONCLUSION

Quercetin is a flavonoid present in many vegetables, fruits and beverages. Due to its anti-oxidant, anti-tumor and anti-inflammatory activity, quercetin has been studied extensively as a chemoprevention agent in several cancer models. Since most of these studies used higher doses of quercetin than clinically achievable, the researchers must focus on the effectiveness of physiologically relevant doses of quercetin. A low dose of quercetin exerted cancer cell-specific inhibition of proliferation and this inhibition resulted from cell cycle arrest at the G1 phase. As a Bioenhancer agent quercetin is capable of enhancing bioavailability and bioefficacy of a particular drug with which it is combined, without any typical pharmacological activity of its own at the dose used.

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