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# "Rutin And Chrysin: Natural Flavonoid Anxiolytics And Their Diverse Pharmacological Properties "

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***Abstract*:** Flavonoids represent a diverse class of plant-derived compounds with significant therapeutic potential. This review focuses on two prominent flavonoids such as Rutin and Chrysin which examining their biochemical properties, mechanisms of action and therapeutic applications. Rutin is a glycoside of quercetin, demonstrates notable antioxidant, anti-inflammatory and vasoprotective properties with promising applications in cardiovascular disease, diabetes management and neuroprotection. Chrysin is a naturally occurring flavone which exhibits anticancer, anti-inflammatory and anxiolytic effects through multiple cellular pathways including modulation of apoptosis and inflammation mediators. Recent evidence suggests both compounds may have synergistic effects when combined with conventional treatments. This review synthesizes current research findings, highlighting the molecular mechanisms underlying their biological activities and discussing challenges in their clinical application including bioavailability and delivery systems. Understanding these flavonoid's therapeutic potential could lead to innovative treatment strategies for various pathological conditions.

***Keywords*:** Flavonoids, Rutin, Chrysin, Anti-anxiety, Anxiolytic, Anti-inflammation, Anti-diabetic.

**INTRODUCTION:** Around the world millions of people suffer from mental illnesses. Anxiety is one of the primary problems with mental health and has become a major area of research in the field of psychopharmacology. Around the world, anxiety is 16.6% common and 55 million people suffer from anxiety and depression. Panic disorder with or without agoraphobia, obsessive-compulsive disorder (OCD), social anxiety, generalized anxiety disorder (GAD), particular phobia and post-traumatic stress disorder (PTSD) are all considered forms of anxiety. Common signs of anxiety include headaches, sweating, shaking and tense or aching muscles.

Dopamine, serotonin and Gamma Amino Butyric Acid (GABA) are among the CNS neurotransmitters thought to be dysregulated in anxiety. Behavioral interventions, medication therapy and psychotherapy are the current methods used to manage anxiety. It has been demonstrated that cognitive behavior therapy is highly successful in treating anxiety disorders that need ongoing care. The two medications most frequently used to treat anxiety in clinical practice are benzodiazepines and selective serotonin reuptake inhibitors (SSRIs). The two classes did however exhibit a number of negative outcomes including reliance, increased suicidal thoughts, sexual dysfunction, decreased alertness and high expense.[1] Numerous mental and physical symptoms including elevated heart rate, cramping in the stomach, sweating, bronchitis, motion sickness,

exhaustion, urination, a state of apprehension and anxiety, failure to fulfill a role, uncertainty about the future, the expectation of a sad event, difficulty concentrating and poor sleep are signs of anxiety.[2]

Nonetheless, new insights into the prevention and/or treatment of anxiety and depression have been brought about by the recent discoveries of a connection between oxidative stress and psychological stress as well as mood disorders.[3]

Many medications used in modern medicine that are either directly or indirectly derived from natural sources come from plant derived components. Because of their inherent diversity and fewer adverse effects, natural compounds are of tremendous interest in the drug discovery process. Despite the fact that a number of natural chemical groups have demonstrated anxiolytic potential.

Flavonoids have been demonstrated to be very selective anxiolytics that do not have any further effects on the central nervous system. They are among the most significant natural products that are widely used worldwide. Higher plants include flavonoids which are low molecular weight substances that exist as secondary metabolites. Flavonoid's diverse chemical structures are responsible for the broad range of biological activity they display. Flavonoids offer a number of benefits including affordability, accessibility, and little adverse effects. Flavonoids have shown promise in both human and animal models.[1]

Antioxidant supplements or a diet high in naturally occurring antioxidants may be able to prevent or treat anxiety and depression. The main class of antioxidants obtained from the diet are polyphenols which include flavonoids and phenolic acids and are well known for their strong antioxidant activity. Utilizing these secondary metabolites of phytochemicals may be a promising strategy for treating and preventing depression and anxiety. Due to their reported wide range of advantageous biological actions including anti-bacterial, anti-viral, anti-inflammatory, anti-allergenic, vasodilatory, anti-mutagenic, anti-depressant and anti-anxiety effects.[3]

**Table no 1: Dietary Polyphenols-Anxiolytic like Effects, Antidepressant like Effects, Side Effects and Dietary Sources [3]**

| Polyphenols | Activity on the Nervous System | Side Effects | Dietary Source |
|---|---|---|---|
| Rosmarinic acid | Anxiolytic like and antidepressant like effects | | Skin of apples |
| Quercetin | Anxiolytic like effects | Sedative effect | Many types of fruits and vegetables (apples, plums, onions, broccoli, tea) |
| Rutin | Anti-depressant like effects | | Many types of fruits and vegetables (apples, plums, cherries, onions, tomato, etc) |
| Chlorogenic acid | Anxiolytic like effects | | Many types of fruits and vegetables (apples, plums, cherries, etc) |
| Caffeic acid | Antidepressant-like effects | | Many types of fruits and vegetables (apples, plums, cherries, kiwi, etc) |
| Apigenin | Anxiolytic-like effects | Slight sedative effect | Parsley and celery |
| EGCG | Anxiolytic-like effects | Sedative and amnesic effects | Tea |

**Neuroanatomy of Fear and Anxiety[4]**

The amygdala plays a key role in processing fear by integrating sensory information, relevance and past experiences to trigger immediate threat responses. It has separate circuits for fear (short, rapid reactions) and anxiety (longer, uncertain responses). Fear related circuits involve the basolateral, central and medial amygdala while anxiety is linked to predictions from the dorsal motor amygdala to the bed nucleus of the stria terminalis. In humans, the medial prefrontal cortex including the orbitofrontal region enhances amygdala activity contributing to the stress response. Increased amygdala responses to threats are common in anxiety disorders even at early stages.

**Currently Marketed Drugs for the Management of Anxiety Disorders[4]**

In the past, tricyclic antidepressants (TCAs) were used to treat anxiety but cognitive behavioral therapy (CBT) has shown comparable effectiveness to SSRIs for severe anxiety and generalized anxiety disorder (GAD). TCAs and MAO inhibitors have side effects like anticholinergic effects, weight gain and low blood pressure. Serotonin reuptake inhibitors (SSRIs) like venlafaxine, phenelzine and Zoloft are safe and effective first-line treatments for anxiety disorders. Duloxetine and other serotonin-norepinephrine reuptake inhibitors (SNRIs) are increasingly popular for treating stress and depression. Both SSRIs and SNRIs work by enhancing neurotransmission improving brain function, reducing anxiety and depression symptoms. Paroxetine's therapeutic effects are linked to improvements in brain structure like new hippocampal cell growth.

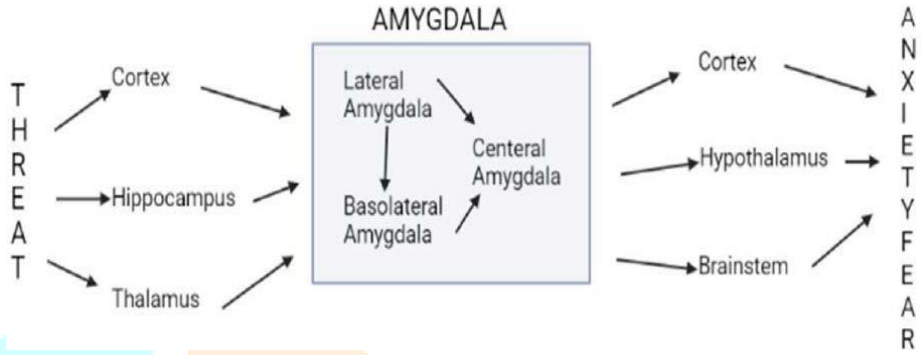


**Figure no 1: Neuroanatomy of fear and anxiety**

**Anti-Anxiety Mechanism[5,6]**

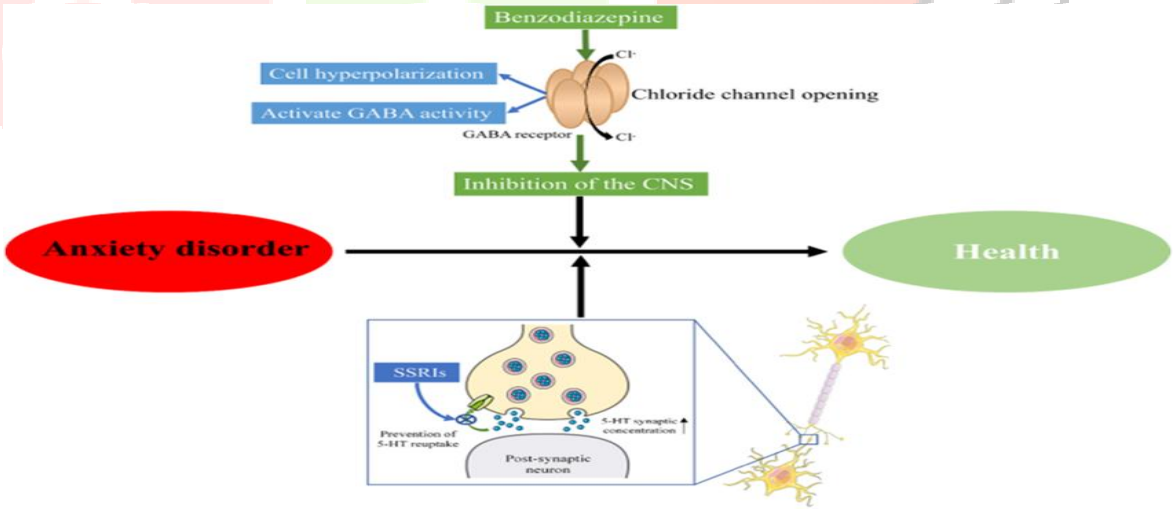


**Figure no 2: Mechanism of anti-anxiety action. CNS, Central Nervous System; SSRIs, selective serotonin reuptake inhibitors**

| Category | Compound | Mechanism |
|---|---|---|
| Flavonoid | Chrysin | As a competitive ligand for benzodiazepine receptors, they enhance the GABAergic neurotransmission by binding to the benzodiazepine drug-receptor of the γ-GABA-benzodiazepine-chloride ion receptor complex |
| | Apigenin | |
| | Apigenin-7-glucose | Acts on GABA receptors |
| | Wogonin | Acts on benzodiazepine receptors for GABA receptors |
| | Baicalein | Acts on non-benzodiazepine receptors for GABA receptors |
| | Baicalin | Acts on non-benzodiazepine receptors for GABA receptors, inhibits the release of glutamate |
| | Luteolin | Acts on benzodiazepine receptors |
| | 6-hydroxy flavone | Acts on benzodiazepines receptors for GABAA-type receptors, enhances GABA activation current |
| | Amentoflavone | Related to ionic GABA receptors |
| | Spinosin | Related to GABA receptors and serotonin receptors |
| Flavonols | Kaempferol | Related to GABAA receptors |
| | Quercetin | |
| | Myricetin | |
| Dihydroflavonoids | Hesperidin | Associated with the serotonin neurotransmitter pathway, acting through its glycosidic ligand hesperidin |
| | Hesperetin | Associated with the serotonin neurotransmitter pathway |

**Figure no 3: Mechanism of anti-anxiety effects of flavonoids**

**Flavonoids**[7]

Plants naturally contain chemicals called flavonoids which aid in growth regulation and the fight against oxidative stress. A broad class of polyphenolic chemicals with a benzo-pyrone structure make up flavonoids. Plants have anticancer properties and are good for heart problems and age-related illnesses. Phenylpropanoid pathway for the biosynthesis of flavonoids. They have been reported to possess several beneficial pharmacological actions such as anti-bacterial when a material was extracted from oranges in 1930 and given the moniker Vitamin P, it was later discovered to be the flavonoid rutin. Since then more than 4,000 flavonoids have been discovered. Flavonoids are chemically composed of a fifteen-carbon skeleton that includes one heterocyclic pyron ring (C) and two benzene rings (A and B). Various kinds of flavonoids exist based on the degree of C ring oxidation and substitution pattern. They consist of the flavones (herperetin, naringenin, and flavon) and the flavonoles (fisetin, kaempferol, quercitin, and myricitin). Individual compounds within a class are distinguished by the degree of substitution of the two benzene rings. Flavonoids are present as aglycones, glycosides, and methylated derivatives. Aglycon is the fundamental structural component of flavonoids. In the case of flavonones and flavonols such as α-pyrone or its dihydroxy derivatives condense the six-membered benzene ring. The C2-C3 double bond and the hydroxyl group at position three distinguish flavonols from flavonones. It has been discovered that several carbohydrates, including D-glucose, galatose, glucorhamnose, arabinose or L rhamnose bind with flavonoids at positions three and seven. The two main absorption bands that flavonoids display are between 320 and 385 nm, which correspond to ring "B" and between 250 and 285 nm, which correspond to ring "A" absorption. A shift of absorption is caused by different functional groups attached to the flavonoid skeleton. For example, quercetin (3,5,7,3´,4´-hydroxyl groups) has a wavelength of 371 nm, kaempferol (3,5,7,4´-hydroxyl groups) has a wavelength of 367 nm and myricetin (3,5,7,3´,4´,5-hydroxyl groups) has a wavelength of 374 nm. Band II absorption includes toxifolin (285), naringenin (288).

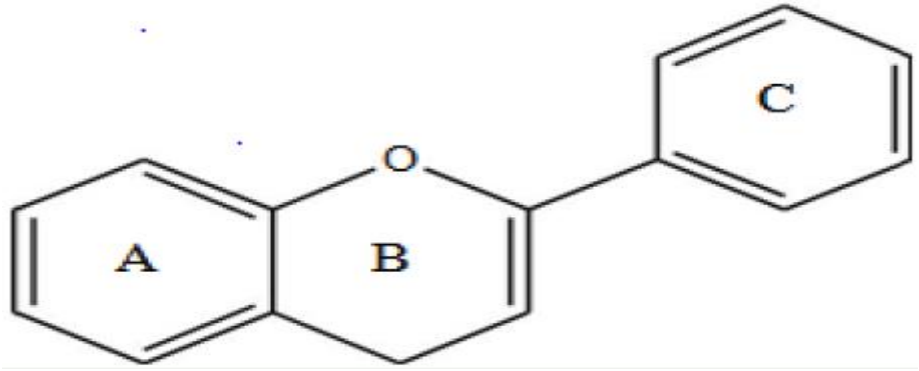


**Figure no 4: General structure of flavonoid**

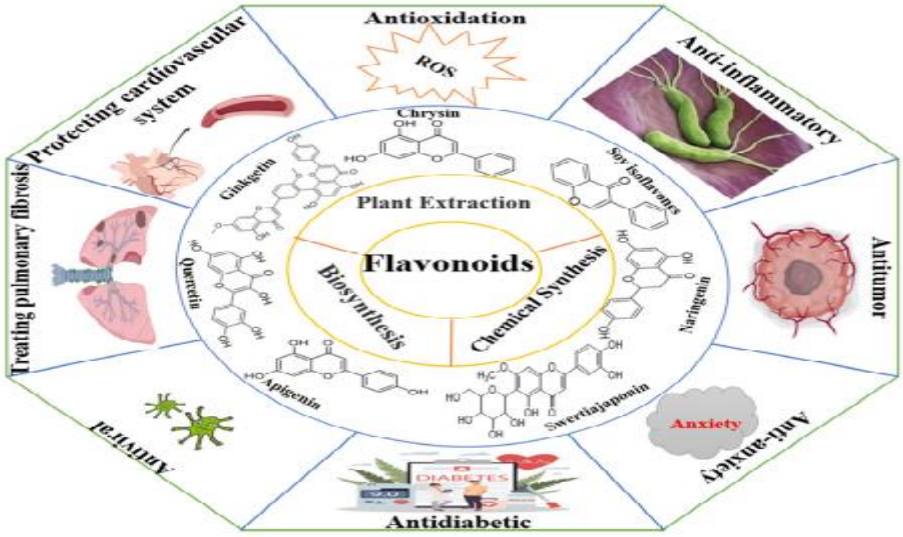


**Figure no 5: Flavonoids have wide range of biological activities.**

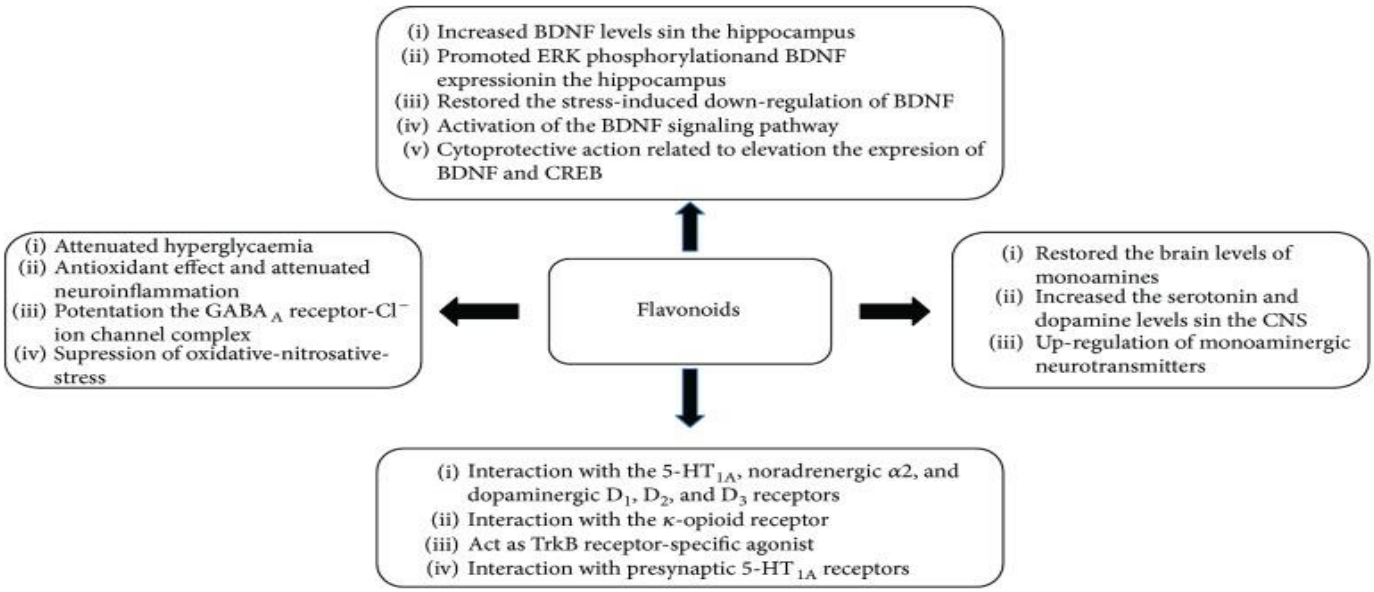


**Figure no 6: Possible mechanism of action of flavonoids with anti-depressant activity**

## Metabolism of Flavonoids[8]

Flavonoid's physiochemical characteristics including lipophilicity, pKa, solubility, configuration and molecular size, determine how well they are absorbed in the intestine from food. Most flavonoids are absorbed in the small intestine while very few are absorbed in the colon. Flavonoids that include sugar components need to be changed into aglycon before they can be absorbed. The intestinal Na+ glucose transporter carries quercetin which is hydrophilic by nature through the small intestine. Another process states that the aglycon component of glycosidic flavonoids is released from brush border cells via lactase phloridzin hydrolase. Flavonoids are converted to various groups in the liver via sulfation, glucoronidation or methylation or they undergo metabolism to form small phenolic compounds. The bioavailability of flavonoids differs depending on where they come from; for instance, onions absorb quercitin more easily than tea or apples do. The flavonoid ring structure of the flavonoids produced in the bile and those not absorbed in the small intestine is broken down by the bacteria in the colon. Oligomeric flavonoids are converted to dimeric and monomeric flavonoids by the stomach's acidic environment. Isoflavones have the highest bioavailability of any flavonoid category.

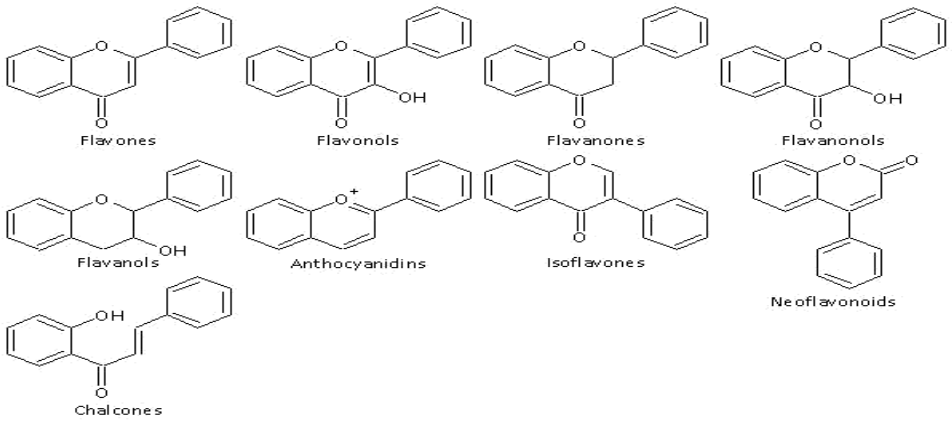


**Figure no 7: Classification of flavonoids**

**Table no 2: Name of flavonoids and its plant source**

| Sr. No | Flavonoid | Plant source |
|---|---|---|
| 1 | Gossypin | Gossypium indicum, Vitifolius and Hibiscus esculentus, Hibiscus Vitifolius |
| 2 | Myricitin | Physalis peruviana Linn. |
| 3 | Naringin | Citrus grandis |
| 4 | Luteolin | Elsholtzia rugulosa |
| 5 | Kaempferol | Apocynum venetum, TeliaSpp |
| 6 | Wogonin | Scutellaria baicalensis |
| 7 | Chrysin | Jatropha cilliata |
| 8 | Apigenin | Chamomile tea |
| 9 | Quercetin | Poacynum hendersonii, Telaispp |
| 10 | Rutin | Physalis peruviana Linn |

**Anxiolytic Flavonoids**

**a) Gossypin, Myricitrin, and Naringin[8]**

Flavonoids like naringin, gossypin and myricetin reduce anxiety at doses below 3 mg/kg with no muscle relaxant effects at lower doses but mild sedative effects at higher doses. Studies in mice show increased open arm entries and time spent in the open arm of the elevated plus maze supporting their anxiolytic potential. Myricitin showed the most pronounced effect at 1 mg/kg with higher doses (up to 30 mg/kg) causing myorelaxant effects in 27% of mice. Naringin and gossypin also exhibited anxiolytic effects with larger doses inducing sedative effects. These flavonoids likely act through GABA receptors and modulate inwardly rectifying potassium channels (GIRK) and hERG potassium channels.

**b) Quercetin[8]**

Quercetin (3,5,7,3′,4′-pentahydroxyflavone) is a polyphenolic flavonoid found in various fruits, vegetables and plants like Telia species. It is commonly consumed in the human diet and is known for its potent antioxidant and anxiolytic (anti-anxiety) properties. Quercetin scavenges free radicals inhibits enzymes that generate reactive oxygen species (ROS) and prevents oxidative stress-induced neuronal damage. Studies suggest a strong link between its antioxidant effects and anxiety reduction which improve cognitive function and help prevent stress-related disorder. Quercetin, along with other flavonoids like rutin and hyperoside exhibits anxiolytic effects similar to diazepam and buspirone. Quercetin has been found to reduce anxiety, enhance memory and modulate the Hypothalamic-Pituitary-Adrenal (HPA) axis which plays a key role in stress responses. In animal studies, quercetin increased social interaction time, improved memory and reversed CRF (Corticotropin-Releasing Factor)-induced anxiety and depression. Glycosidic attachments to quercetin influence its pharmacokinetics but aren't essential for its anxiolytic effects.

c) **Apigenin-glycoside**[8]
Apeginin-7-glycosideis found in many plants such as *Stachys tibetica*. It is a flavonoid having anxiolytic activity affecting GABA receptor function. Apeginin 7-glycoside have anxiolytic action. They isolated apeginin 7-glycoside from *S. tibetica*. They used albino rates of both sexes 150-200 g in weight. Acute toxicity of the compound was checked and 2.5mg/kg dose of the compound was selected for studying anxiolytic activity. Diazepam was used as a positive control. Apegenin 7-glucoside was suspended in sodium carboxy methyl cellulose and control group received aqueous sodium carboxy methyl cellulose (1%). Elevated plus maze test showed anxiolytic activity of apigenin 7-glucoside as evident from an increase in number of open arm entries and decrease in number of close arm entries.

**d) Naringin**[8]
Naringenin (4',5,7-trihydroxyflavanone) found in citrus fruit peels is known for its neuroprotective and anxiolytic properties. It has monoamine oxidase inhibitory activity and benzodiazepine receptor binding affinity which may help protect against neurodegenerative conditions like depression and anxiety. Naringin also shows anxiolytic effects in animal models such as male rats in the elevated plus maze test. Although it doesn't modulate the GABA-A benzodiazepine receptor, naringin produces anxiolysis through other mechanisms. Studies suggest that naringin's anxiolytic effects are distinct from those of traditional benzodiazepines like midazolam.

e) **Chrysin**[8]
Chrysin (5,7-dihydroxyflavone) is found in many naturally occurring plants and has anxiolytic activity. Benzodiazepines are used for relieving anxiety but are associated with several side effects such as amnesia. Some naturally occurring flavonoids have anxiolytic action but are not associated with some effects associated with benzodiazepines such as sedation, myorelaxation and anti-convalsant effects therefore have shown selectivity in treating anxiety. These flavonoids are considered partial agonist of benzodiazepine receptor. The effect of chrysin on rats 70-90 days old having weight 240-280 g for anxiolytic activity. Elevated plus maze showed anxiolytic potential of chrysin. Other effects of chrysin along with anxiolytic activity such as amnesia and hypnosis. Diazepam 2 mg/kg was given to animals for avoidance test. Diazepam increased inhibitory avoidance, sleep down latency and decrease locomotor activity and decrease retention of habituation to the open field. Tail flick test showed analgesic action of diazepam but had no effect on memory enhancing effect of chrysin. Chrysin has anxiolytic activity with no side effects associated with diazepam.

f) **Rutin**[8]
Rutin is an important flavonoid found in many plants. It has been shown to have excellent anxiolytic potential. *Hypericum perforatum* has been used for centuries for many CNS problems such as anxiety, sleep disorder or depression. It has been shown that SJW is rich source of flavonoids having prominent action on GABA-A, GABA-B and glutamine receptors inhibition of monoamine oxidase A and B and also inhibition of reuptake of serotonin noradrenaline and dopamine. This plant contains many classes of flavonoids such as amentoflavon, quercitin and rutin. Gobbi and and Mennini have reviewed flavonoids where they have shown molecular mechanisms of flavonoid binding to its receptors for relieving anxiety.

**g) Baicalein**[2]
Baicalein is a trihydroxyflavone flavonoid which has hydroxyl molecules at carbon atoms 5, 6, and 7. Baicalensis is the flavonoid that is most active. According to multiple sources, baicalein is a powerful molecule that has properties similar to antioxidant and free radical scavenging. This flavone crosses the blood-brain barrier and has notable relaxing and central nervous system depressive effects. Purified from the ethanolic extraction of the Scutellaria root, baicalein may suppress the brain, lower prostaglandin E2 levels in the brain act as a strong antioxidant and stop the onset of depression in rats. Six out of 48 rodent brains had lower levels of prostaglandin E2 in their brains. This compound also acts as a strong antioxidant and helps regulate mice's chronic stress behavior.

**h) Myricetin**[2]
Hydroxyl groups have been substituted at carbon atom positions 3, 3′, 4′, 5, 5′, and 7 in hexahydroxy flavone myricetin. There is an abundance of various things such as tea, rum, dried fruits and vegetables. It has been shown to have antidepressant, analgesic and antitumor properties. According to a study, myricetin decreased

behavior in stressed mice as the FST had predicted. The discovery that myricetin reduced corticosterone plasma levels which increased brain activity of the reactive oxygen species enzyme and raised BNF levels strengthened the flavonol's potential as an antidepressant.

**Table no 3: Affinity of natural flavonoids for the benzodiazepine receptors**

| Name | Structure (Monoflavonoids) | Ki (mm) |
|---|---|---|
| Flavone | 2-Phenylchromone | 1 |
| Norwogonin | 5,7,8-Trihydroxyflavone | 0.88 |
| Chrysin | 5,7-Dihydroxyflavone | 3 |
| Apigenin | 5,7,40-Trihydroxyflavone | 3 |
| Naringenin | 5,7,40-Trihydroxyflavanone | >25 |
| Flavanone | 7,30-Dihydroxyisoflavan | >40 |
| Myricetin | 3,5,7,20,40-Hexahydroxyflavone | >100 |
| Acacetin | 5,7-Dihydroxy-40-methoxyflavone | >100 |
| Quercetin | 3,5,7,30,40-Pentahydroxyflavone | >100 |
| Rutin | 5,7,30,40-Tetrahydroxyflavone-3-O-Glc-Rha | >100 |

**Flavonoids Affinity for GABA Receptor[8]**

GABA plays an important role in anxiety. Benzodiazepine binds with GABA receptor mediating anxiety. The compounds having affinity for the GABA receptor and believed to play an important role in anxiety. Experiment in transgenic animals (mice) both knock-in and knock out showed that GABA has various receptors subtypes and each of them plays different physiological roles. Comparing mutant and wild types mice have shown different responses to diazepam indicated from their behavior studies; GABA receptors containing α1-subunits mediate sedation and serve as targets for hypnotic and sedative actions while α2- and α3-containing receptors mediate anxiolysis while α5-containing receptors are associated with memory. 6-hydroxyflavone act as a subtype selective partial positive allosteric modulator at the flumazenil-sensitive benzodiazepine site. 6-Hydroxyflavone exhibit significant preference for α2- and α3- compared to α1- and α5-containing receptors expressed in HEK 293T cells. *In vivo*, 6-hydroxyflavone displayed anxiolytic effects in the elevated plus-maze test, with no sedation, myorelaxation, cognitive impairment, anticonvulsant or motor in-coordination effects at anxiolytic doses.

- **Rutin[9]**

**Rutin:** ‘Rutin is derived from the plant Ruta graveolens (common Rue), which contains rutin in its aerial portions. More than seventy plant species and plant-based foods including buckwheat seeds, apricots, cherries, grapes, onions, plums and oranges which contain rutin. It is a kind of flavonoid glycoside also referred to as vitamin P or purple quercitrin. In the 19th century, it was initially found in buckwheat (Fagopyrum esculentum). Ruta graveolens L. (Rutaceae), Sophora japonica L. (Fabaceae), Maranta leuconeura E. Morren (Marantaceae), Orchidantha maxillarioides (Ridl.) Schum (Lowiaceae), Strelitzia reginae Banks ex Aiton (Strelitziaceae), Eucalyptus spp. (Myrtaceae), Labisia pumila (Blume) Mez (Primulaceae) are the top plants that contain up to 1.5% of rutin.


**Figure no 8: A- Plants of Ruta graveolens, B- its flowers, C- its Leaves**

**Chemistry and pharmacology of rutin**

Rutin (3,3′,4′,5,7-penta hydroxyflavone-3-rhamnoglucoside) also called as rutoside, quercetin-3-rutinoside or sophorin is a flavonol category of flavonoid.

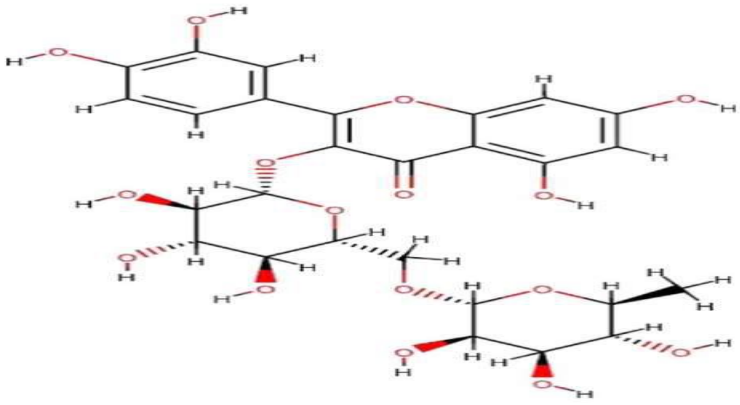

**Figure no 9: Structure of Rutin**

**Table no 4: The physicochemical properties of rutin**

| | |
|---|---|
| Chemical formula | $C_{27}H_{30}O_{16}$ |
| Molar mass | 610.52 g $mol^{-1}$ |
| Form and color | Powder, yellow to green |
| Melting point | 242 °C |
| Solubility in water | 12.5 mg/100 mL |
| Site of absorption | Intestine |
| Excretion | Urine (about 10%); unchanged in faeces (rest) |

**Natural Occurrence and General Pharmacological Effects of rutin[10]**

The presence, nature and location of glycosylation are among the structural differences that cause major differences in the metabolism, absorption and antioxidant activity of flavonoids. One of the most powerful antioxidants among phytochemicals with anticancer properties is rutin (3,3′,4′,5,7-pentahydroxyflavone-3-rhamnoglucoside) which also has certain additional biochemical actions in the prevention and treatment of cancer.

Rutin is frequently referred to as vitamin P because of these biological actions. Rutin is a structural component of around 130 medicinal medications that have been developed. It is commonly used as medicine in China and can be found in plants including apples, buckwheat and green tea. One of the main sources of rutin is buckwheat. The history of rutin derived from the buckwheat plant dates back to the 1940s, when the plant was utilized in American medicine.

Interestingly, the plant's leaves and flowers had the highest concentration, accounting for around 2–10% of the total weight of the plant. The amount of rutin present in different plant portions is mostly determined by the plant's genetic type and geographic origin. Ruta graveolens L. (Rutaceae), Sophora japonica L. (Fabaceae), Strelitzia reginae Banks ex Aiton (Strelitziaceae), Maranta leuconeura (Marantaceae), Orchidantha maxillarioides (Lowiaceae), Eucalyptus spp. (Myrtaceae), Canna indica L. (Cannaceae), and more than 70 plant species have been shown to be good sources of rutin.

**Biological effects of rutin[9]**

Rutin is a common dietary flavonoid usually nontoxic naturally derived compound exhibits a diverse range of useful biological properties such as anticancer, antioxidant, antidiabetic, anti-inflammatory, anti-bacterial, anti-fungal, neuroprotective, cardioprotective, hepatoprotective, nephroprotective, haematoprotective, antiarthritis, anthelmintic, testicular protection etc. The brief details of the main biological properties of rutin are described below.

**a) Anticancer property[9]**

Rutin is a flavonoid which has demonstrated significant anticancer, chemopreventive and chemosensitizing properties across various cancer types. Studies show that rutin inhibits tumor growth in human leukemia, neuroblastoma, colon adenocarcinoma and other cancer cell lines. It works by inducing cell cycle arrest, apoptosis and reducing tumor cell proliferation. Rutin has also shown antitumor effects in animal models such as reducing leukemia tumor growth and enhancing macrophage phagocytosis. When combined with chemotherapy agents like cisplatin and cyclophosphamide rutin enhances their effectiveness. Additionally, rutin has exhibited chemopreventive activity in skin and colon cancer models and boosts antioxidant defenses in cancer cells.

**b) Antioxidant property[9]**

Antioxidants like rutin is inhibit oxidation and protect cells from damage caused by free radicals. Rutin known for its strong antioxidant properties, scavenges free radicals and prevents lipid peroxidation. It improves antioxidant defenses, especially in conditions like iron overload-induced hepatic oxidative stress. Rutin works by donating electrons, scavenging hydroxyl radicals and reducing reactive oxygen species (ROS). It also enhances antioxidant enzymes and reduces harmful substances like malondialdehyde (MDA) and nitric oxide (NO). Additionally, rutin protects against radiation-induced DNA damage by scavenging free radicals and mitigating oxidative stress.

**c) Antidiabetic property[9]**

Diabetes is a chronic condition characterized by high blood sugar due to insufficient insulin production or ineffective use of insulin. Flavonoids such as rutin have beneficial effects on diabetes by improving glycemic control, lipid profiles and antioxidant levels. Rutin's anti-hyperglycemic effects include reducing carbohydrate absorption, inhibiting gluconeogenesis, increasing glucose uptake and stimulating insulin secretion. It also protects pancreatic beta cells and improves liver function. Rutin helps prevent diabetic complications by reducing oxidative stress, inflammatory cytokines and advanced glycation end products. It enhances insulin secretion and glucose utilization making it a potential treatment for Type 2 diabetes.

**d) Anti-inflammatory property[9]**

Inflammation is a protective response to harmful stimuli and flavonoids like rutin have been shown to reduce the risk of chronic and cardiovascular inflammatory diseases. Rutin's radical scavenging and anti-inflammatory effects aid in healing conditions like ulcerative colitis. Studies indicate rutin can treat severe vascular inflammatory diseases by inhibiting the HMGB1 protein signaling pathway. Additionally, rutin-rich extracts from tartary buckwheat sprout (TBS) show stronger anti-inflammatory effects compared to common buckwheat sprout (CBS). Encapsulated rutin also enhances anti-inflammatory activity by inhibiting pro-inflammatory mediators like IL-6 and NF-kB.

**e) Anti-bacterial property[9]**

Bacterial infections such as pneumonia, sepsis and gonorrhea, it can cause severe diseases in humans. Rutin exhibits strong antibacterial activity. Studies show that rutin is effective against various bacteria including *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Streptococcus pyogenes* and *Escherichia coli*. When combined with other flavonoids like quercetin, morin and quercitrin, rutin enhances antibacterial effects, showing synergy with antibiotics against *Methicillin-resistant Staphylococcus aureus* (MRSA). Rutin also inhibits biofilm formation in *Streptococcus suis* making it a potential natural agent for preventing biofilm-related infections. Additionally, rutin has been found in antibacterial honey from stingless bees.

**f) Neuroprotective property[9]**

Rutin is demonstrates strong neuroprotective effects against various neurodegenerative diseases including Alzheimer's and Parkinson's disease. It combats neuroinflammation, oxidative stress and neuronal damage through its antioxidant and anti-inflammatory properties. Rutin has been shown to enhance antioxidant enzyme activity, reduce lipid peroxidation and improve neurotrophic factors like BDNF and NGF in diabetic retinas. It also protects against neurotoxicity induced by substances like cisplatin and fluoride improving memory and cognitive function in animal models. Additionally, rutin inhibits prion protein accumulation, decreases apoptosis and modulates key neuroprotective genes offering potential as a therapeutic agent for neurodegenerative conditions.

- **Chrysin[11]**

**Chrysin:** Dietary supplements from plant origin possess many pharmacological properties and they are able to protect and cure diseases in humans and animals. Flavonoids constitute a group of important bioactive substances found in plants. Flavonoids are polyphenolic compounds which are the most wide spread chemical class of phytochemicals especially those that have a multitude of health-beneficial effects. Flavonoids are widely found in plants. Dietary sources of flavonoids include vegetables, spices, fruits and seeds. These substances appear to be credible to consume in the diet. A diet rich in flavonoids is thought to be beneficial. Flavonoids are recognized as important components used in different pharmaceutical, nutraceutical, medical and cosmetic applications. The effects of flavonoids are attributed to their anti-oxidant, anti-mutagenic, anti-inflammatory and anti-carcinogenic properties as well as their ability to modulate essential cellular enzyme functions.
Chrysin is a phytochemical that has promising pharmacological and beneficial bioactivity which is categorized under the flavonoids class. It is widely used in the treatment of different degenerative disorders. Within the scope of this review, some current information about the structure, mechanism of action, important pharmacological properties of chrysin and its effects on human and animal health have been compiled.

**Sources of Chrysin[11]**
Chrysin is a phytochemical found in mainly propolis, honey and some plant extracts, such as blue passionflower (*Passiflor acaerulea*). High levels of chrysin have been described in honey and propolis. In addition, mushroom such as *Pleurotus ostreatus* and *Radix scutellariae* are important chrysin sources. Propolis shows many biological activities such as anti-inflammatory, antitumor, antioxidant, antibacterial, antifungal and antiviral activities. Some of these effects have been reported to be due to chrysin found in propolis. Studies have also shown that amount of chrysin in propolis is up to 28 g / L. It was accounted for that chrysin content could be found as 5.3 mg / kg in forest honey and 0.10 mg / kg in honey. It has also been stated that various mushrooms from Lesvosisland in Greece contain chrysin and the level of chrysin individually varies between 0.17 mg / kg in Lactarius deliciosus and 0.34 mg / kg in Suillus bellinii.
Another important source of chrysin is Passiflora plant which belongs to Passifloraceae family (Passion flower family), that contains about 500 species. Chrysin extract obtained from the genus Passiflora was shown to have anti-depressive, anxiolytic, sedative, anti-spasmolytic, anti-asthmatic effects and shows protective effects on sleep and respiratory disorders. Chrysin is a naturally occurring monovalent in Passiflora caerulea is a ligand for central and peripheral benzodiazepine receptors.

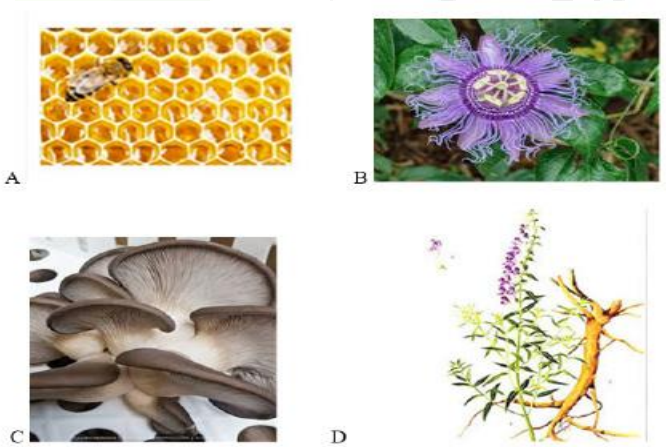


**Figure no 10: Chrysin sources: A. Propolis, B. Passiflora Sp., C. Pleurotus ostreatus, D. Radix scutellariae.**

**Chemical Structure**[11]

Chrysin is a natural polyphenolic compound consisting of 15 carbon skeletons. Structurally chrysin consists of 2 benzene rings (A, B) and 1 oxygen-containing heterocyclic ring (C). While the 3rd carbon lacks the hydroxyl group, it has 2-3 double-bonded carbons with one carbonyl group connected to the 4th carbon. Chrysin contains 2 fused rings A and C and a phenyl ring B. A ring posseses the flavone structure having an extra hydroxyl group. Chrysin is classified within the flavones. It has also –OH groups on the 5th and 7th carbon atoms. Different from other flavonoids, chrysin does not have any oxygen containing groups in ring-B. Primarily, the diference in A ring oxygenation give rise to chyrsin derivatives (wogonin, oroxylin A and baicalein). Chrysin ($C_{15}H_{10}O_4$) is derived from phenylalanine. Phenylalanine is initially converted into cinnamic acid by the action of phenylalanine ammonia-lyase enzyme. A series of enzymatic reactions then produce chrysin.


**Figure no 11: Structure of Chrysin (5,7-Dihydroxyflavone)**


**Figure no 12: Derivatives of Chrysin**

**Pharmacokinetics**[11]

Flavonoids are metabolized in the gastrointestinal lumen, intestinal wall cells and liver. One characteristic shared by flavonoids is their presence in the bloodstream as conjugates of glucuronide and sulphate. The liver and small intestine are where flavonoid conjugation occurs. The process involves sulfation, glucuronidation and methylation. This detoxification process limits their potential toxic effects and facilitates the elimination of chyrisin via bile and urine by increasing their hydrophilicity. Flavonoids are secreted via bile into the duodenum. It undergoes enzymatic degradation by glucoronidase in the distal parts of intestines which can then be reabsorbed. Flavonoids may remain in the body for a longer amount of time as a result of enterohepatic recycling.

Chrysin's therapeutic effects rely on its bioavailability, the compound’s solubility and the concentrations that may be achieved in vivo. The intestinal absorption of chyrsin is low. The administration of a single oral dose, plasma quantities of unaltered chrysin were extremely low. Because of its limited intestinal absorption, chyrsin's maximum concentration in serum ranges from 12 to 64 nm. Chrysin has a 99% binding rate to plasma proteins. Chrysin's oral bioavailability ranged between 0.003-0.02%. Chrysin therapy can often be used in the micromolar range.

**Toxicological Effects**[11]

It was reported that flavonoids are highly effective at low doses but when consumed in excess or in higher amounts, they can have toxic effects on the human body. In this context, effective doses to be taken daily are important in order to obtain useful effects and to prevent toxic situations. 0.5 to 3 g chrysin is recommended for daily intake. On the other hand, it can induce liver cell toxicity even at daily concentrations.

Chrysin's cytotoxic effects are linked to its peroxidase-like activity in hepatocytes which produces harmful byproducts. Chrysin de novo decreases cell counts and has an impact on DNA synthesis. Myeloperoxidase is thought to be the primary cause of chrysin toxicity in neutrophils.

**Pharmacological effect of Crysin[11]**

Chrysin shows many pharmacological effects such as Antioxidant effect, Neuroprotective effect, Anti-inflammation effect, Anxiolytic effects, Protective effect in Cardiovascular Diseases, Anti-osteoporotic effect.

**a) Antioxidant Effect[11]**

Chrysin is effectively scavenges reactive oxygen species (ROS) and reduces oxidative stress by stimulating antioxidant enzymes like glutathione peroxidase, catalase and superoxide dismutase. It protects cells from oxidative damage including lipid peroxidation and DNA damage. In animal studies, chrysin prevented oxidative stress and organ damage caused by cisplatin and methylmercury exposure by inhibiting key enzymes like xanthine oxidase. Chrysin also protected the reproductive system and enhanced sperm quality in varicocele-induced infertility, demonstrating its promise as an antioxidant and protective agent in a number of oxidative stress-related disorders.

**b) Neuroprotective Effect[10]**

Chrysin has shown neuroprotective and anti-inflammatory effects, particularly in neurodegenerative diseases like Parkinson's disease and Alzheimer's disease. It suppresses microglial activation by inhibiting pro-inflammatory cytokines (e.g., nitric oxide, TNF-α, IL-1) and enzymes like iNOS and COX-2. Chrysin also blocks key inflammatory pathways (NF-κB, JNK) which reducing neurotoxicity in microglial cells. Through the enhancement of antioxidant and anti-apoptotic action, it improves cognitive and motor function in individuals with spinal cord injury (SCI) and traumatic brain injury (TBI). Additionally, chrysin-loaded solid lipid nanoparticles alleviated neuronal damage in Alzheimer's by increasing antioxidant levels and reducing memory loss.

**c) Anti-inflammatory Effect[11]**

Chrysin exhibits anti-inflammatory effects through agonistic activity on PPARγ, downregulating iNOS and COX-2 production. It inhibits COX-2 and shows weak interaction with COX-1. Chrysin reduces inflammation in chronic asthma by decreasing inflammatory cell infiltration and respiratory tract inflammation. Chrysin decreased glial cell count, infarct volume and neurological problems in a mouse model of cerebral ischemia while blocking pro-inflammatory cytokines (e.g., IL-1, IL-6, and TNF-α) and inflammation markers (NF-κB, COX-2, and iNOS).Its anti-oxidative and anti-inflammatory properties make chrysin a potential candidate for treating cerebral ischemia/reperfusion injury.

**d) Protective Effect in Cardiovascular Diseases [11]**

Numerous flavonoids and other polyphenols have been demonstrated to have positive impacts on cardiovascular disease and cancer chemopreventive qualities in both people and animals. Chrysin have antiplatelet activity. Nevertheless, the mechanism resulting in the inhibition of platelet function is unknown. In a study conducted on 16 healthy volunteers, chrysin was reported to inhibit platelet aggregation and granule production induced by ADP and U46619. Chrysin inhibits collagen-induced activation of PLCγ2, Akt, Syk, phosphorylation of ERK1 and PKK according to biochemical testing. Chrysin has been shown to significantly inhibit platelet aggregation and secretion in vitro as well as decrease platelet adherence and spreading to the fibrinogen-coated surface. The effect of chrysin against doxorubicin (DOX)-induced cardiotoxicity. Chrysin significantly ameliorated myocardial damage such as conduction abnormalities, increased lactate dehydrogenase and serum creatine kinase-MB isoenzyme. In addition, while DOX decreased Bcl-2 expression, it caused apoptotic tissue damage by increasing Bax and cytochrome c expressions and caspase-3 activity. Chrysin pretreatment significantly improved these apoptotic effects of DOX. Overall, the results show that chrysin has a strong protective effect on cardiotoxicity induced by doxorubicin via decreasing oxidative stress, inflammation and apoptotic tissue damage.

**e) Anti-osteoporotic effect[11]**

Chrysin at 50 and 100 mg/kg has been demonstrated in a recent study to have a possible anti-osteoporotic effect by increasing bone mineral content and decreasing excessive alterations in bone-remodeling markers in rats with ovariectomies. Additionally, chrysin enhanced the function and sensitivity of estrogen receptors, exhibiting an action similar to that of estrogen. Furthermore, chrysin at these doses raised femur dry weight, femur ash weight, bone ash calcium and phosphorous levels in a dose-dependent manner while preventing body weight gain and uterine weight loss.

**f) Anxiolytic-like Effects of Flavonoid Chrysin[12]**

Chrysin exhibits anxiolytic-like effects in various animal models, including mice, rats and zebra fish. A single dose of 1 mg/kg chrysin increased time spent in open arms in the elevated plus maze (EPM) and the illuminated compartment in the light/dark box (LDB) similar to diazepam without causing typical benzodiazepine-induced sedation. These effects were blocked by flumazenil suggesting that chrysin acts on the GABA/benzodiazepine receptor complex. Additionally, chrysin reduced anxiety-like behavior in female rats during low steroid hormone phases (e.g., metestrus–diestrus) and in a surgical menopause model without the sedative side effects of benzodiazepines. This supports the potential of chrysin as an alternative anxiolytic, though further studies are needed to explore its mechanisms, including possible involvement of other neurotransmitter systems or anti-inflammatory effects.[11]

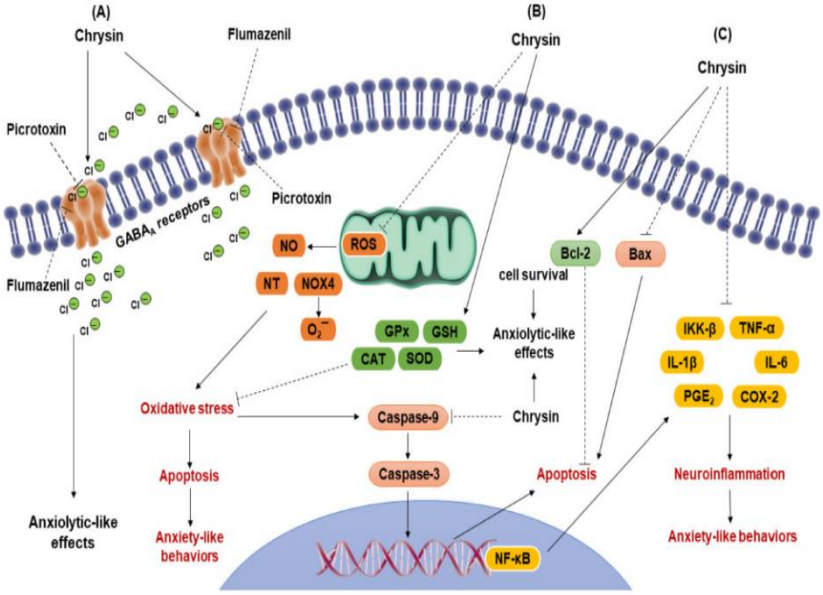


**Figure no 13: Mechanism of action of the flavonoid chrysin potentially involved in its anxiolytic-like effects**

**g) Antidepressant-like Effects of Flavonoid Chrysin[12]**

Chrysin shows promise as an antidepressant with studies indicating positive effects in various preclinical models. In female C57B/6J mice, chrysin (5–20 mg/kg) improved behavior in the tail suspension test (TST), increased serotonin, BDNF and NGF levels and reduced pro-inflammatory cytokines. Similarly, male mice with depression from olfactory bulbectomy showed antidepressant-like responses after 20 mg/kg chrysin, with changes in serotonin and cytokine levels. Chrysin also affected serotonin receptors in Wistar rats, resembling fluoxetine's effects. In a menopause model, chrysin (1 mg/kg) induced depression-like behavior similar to neurosteroids and its antidepressant effects seem mediated by the GABAergic system.

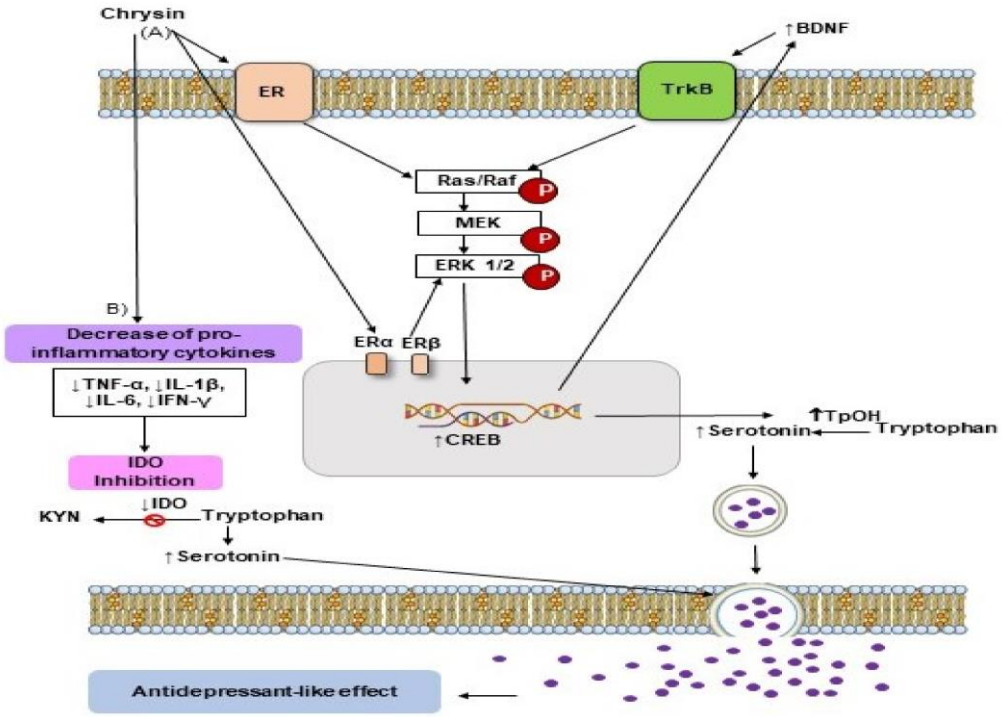


**Figure no 14: Possible mechanisms of action involved in the antidepressant-like effect of chrysin**

## CONCLUSION

The extensive review of current research on rutin and chrysin underscores their significant potential as therapeutic agents across multiple pathological conditions. The multifaceted biological activities of these flavonoids demonstrate their versatility in medical applications. Rutin's pronounced antioxidant and anti-inflammatory properties, coupled with its cardiovascular protective effects, position it as a promising candidate for treating various chronic diseases. Its ability to modulate glucose metabolism and enhance insulin sensitivity further highlights its potential in diabetes management. Chrysin's remarkable anticancer properties, particularly its ability to induce apoptosis in various cancer cell lines while showing minimal toxicity to normal cells, warrant continued investigation. Its anxiolytic and anti-inflammatory properties add to its therapeutic value, suggesting potential applications in neurological and psychiatric disorders. However, several challenges must be addressed before these compounds can be fully utilized in clinical settings. The primary limitations include their relatively low bioavailability and the need for improved delivery systems. Future research should focus on developing novel formulations and delivery mechanisms to enhance their absorption and bioavailability. Additionally, more comprehensive clinical trials are needed to establish optimal dosing regimens and evaluate potential long-term effects. The synergistic effects observed when these flavonoids are combined with conventional treatments open new avenues for integrated therapeutic approaches. This could lead to more effective treatment strategies with reduced side effects. Furthermore, the natural occurrence of these compounds in common dietary sources suggests potential applications in preventive medicine and nutritional therapy. As our understanding of the molecular mechanisms underlying their biological activities continues to grow rutin and chrysin may emerge as valuable tools in the therapeutic arsenal against various diseases. Their natural origin combined with their broad spectrum of biological activities and relatively low toxicity makes them particularly attractive for drug development and therapeutic applications.

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