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PHYTOCHEMICAL AND NEUROPHARMACOLOGICAL BASIS OF *HIPPOPHAE SALICIFOLIA* LEAVES IN ANXIETY DISORDERS: A REVIEW

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ABSTRACT: *Hippophae salicifolia* D. Don, known as Himalayan Sea buckthorn, is a medicinal plant distributed in the Himalayan region. Based on available literature, this plant contains flavonoids, phenolic acids, tannins, triterpenoids, and antioxidant vitamins. Most research has been done on the fruit and seed oil. There is limited research published on the leaves and their pharmacological properties. The purpose of this review is to summarize the phytochemical and neuropharmacological activities of *H. salicifolia* leaves and evaluate their potential role in the management of anxiety disorders. The available literature systematically collected and reviewed to evaluate the phytochemical profile, experimental pharmacological evidence and possible mechanisms associated with the leaves of *H. salicifolia*. Studies on *H. salicifolia* leaves reported antioxidant, anti inflammatory, and adaptogenic effects. Some experimental reports also indicate that leaf extract may reduce changes in physiology related to chronic stress. As oxidative stress, neuroinflammation, and HPA-axis disturbance are linked to anxiety disorders, the phytochemicals present in the leaves may be relevant for neuropharmacological research. However, direct evidence supporting anxiolytic activity remains limited. The available data shows that *H. salicifolia* leaves may have potential effects on the nervous system and could serve as a promising source of bioactive compound in anxiety disorder. Still, we need pre-clinical studies and human trials to prove if they really work for anxiety and to understand how they work.

INTRODUCTION: Anxiety disorders are common mental health problems across the world and affect millions of people. The main features of anxiety are persistent fear, excessive worry, and behavioral disturbances that interfere with normal daily life. Anxiety often coexists with depression, poor sleep and thinking problems, this makes management difficult and puts more load on health systems¹.

Long term stress is major problem for anxiety. When stress goes on for long the HPA axis does not work normally. This leads to high cortisol for long time such hormonal changes can affect brain cells. It may also lead to changes in parts like hippocampus, amygdala and prefrontal cortex. These areas help to control emotions and thinking²⁻³.

Long stress also affects how the brain adapts it can cause changes in dendrites, less formation of new neurons and weak connections between neurons. This may lead to memory issues and emotional problems, and it can also increase the risk of anxiety²⁻⁴. Another point is oxidative stress. Long stress increases ROS in the body. This can damage lipids, proteins and DNA it may also disturb signals



in neurons and mitochondria; inflammation is also involved in neuronal injury. Studies also reported that level of TNF- α , IL-1 β , and IL-6 also increase in anxiety⁵⁻⁷.

Anxiety disorders are linked to chemical imbalances in the brain involving serotonin, dopamine, and GABA systems disrupt normal mood which regulate and enhance anxiety responses. But standard pharmacological agents such as benzodiazepines and selective serotonin reuptake inhibitors (SSRIs) act on these pathways, their prolonged administration is restricted because of undesirable effects, tolerance, dependence, and withdrawal symptoms⁸⁻⁹.

Regular anti-anxiety drugs come with a lot of drawbacks. That's why researchers are now looking at medicinal plants as an alternative. Plant compounds are being studied a lot for brain and mental health problems. Most of the focus right now is on phytochemicals like flavonoids and phenolic compounds. They're strong antioxidants, anti-inflammatory and they help protect nerve cells. These bioactive constituents not only clearing free radicals but also regulate intracellular signaling pathways involved in neuronal survival, synaptic plasticity, and inflammation, thereby offering a multi-targeted approach for anxiety management¹⁰.

Hippophae salicifolia D. Don, or Himalayan Sea Buckthorn leaves have a lot of active compounds flavonoids, phenols, tannins, and antioxidant vitamins. Experimental investigations show that leaf extracts act as antioxidants, anti-inflammatory, antimicrobials, and Adaptogens. Some early animal studies also suggest they may help reverse the body changes caused by chronic stress. Studies on anxiolytic potential of *H. salicifolia* leaf extracts remain scarce. More pharmacological investigations are required to clarify their neuroprotective potential and therapeutic significance in anxiety management¹¹⁻¹⁵.

Traditional Medicinal uses of *Hippophae salicifolia*: In the traditional healthcare systems of the Himalayan region, *Hippophae salicifolia* has been used for a variety of medicinal purposes. Ethnobotanical reports indicate that its leaves and fruits are commonly employed for relieving headache, severe cold, cough and throat infections.

Berry oil has traditionally been used for managing gastritis, ulcers and certain gynecological infections, while bark ash has been applied to burn wounds and diarrhoea. In addition, berries have also been used in veterinary medicine, highlighting the broad ethnomedicinal importance of this species¹¹.

Phytochemical Profile: The leaf material of *Hippophae salicifolia* D. Don contains a wide range of biologically active phytochemicals, particularly flavonoids, flavonols, phenolic acids, tannins, flavone glycosides, and other polyphenolic molecules. Recent LC-MS investigation revealed numerous phytochemicals that are responsible for the plants antioxidants, anti inflammatory, antimicrobial, and potential neuroprotective activities. The broad spectrum of these phytoconstituents suggests that *H. salicifolia* leaves may represent a valuable natural source of therapeutic agents for managing oxidative stresses-related disorders and other chronic diseases¹⁵.

Flavonoids and Flavonols: Flavonoids constitute one of the predominant groups of phytochemicals in *H. salicifolia* leaves. LC-MS analysis has detected several flavonoids including quercetin, kaempferol-3-O-rhamnoside, isorhamnetin, dihexosylisorhamnetin, 6-hydroxyluteolin-7-rhamnoside, apigenin 4'-O-rhamnoside, and apigenin 6,8-di-C-glucoside. These flavonoids are reported to possess potent antioxidant capacity and may help neutralizing reactive oxygen species (ROS) they also suggested to contribute to the overall pharmacological potential of the plant^{13, 15}.

Phenolic Acids: Phenolic acids represent another important class of bioactive constituent present in *H. salicifolia*. The principle phenolic acids identified include chlorogenic acid, quinic acid, caffeoyl-2-hydroxyethane-1,1,2-tricarboxylic acid, and 3-p-coumaroylquinic acid. These phenolic constituents demonstrate both antioxidant and anti-inflammatory activities and also known to protect cellular components from oxidative damage and contribute to overall tissue protection¹⁵.

Catechins and Polyphenolic Compounds: Several Catechin derivatives including epigallocatechin - 3 - O - gallate (EGCG), methylgalloyl epicatechin, and 3'-O-methylcatechin

have been identified in *H. salicifolia* leaves. These Catechins exhibit strong antioxidant capacity and may help to neutralize free radicals and protecting cells against oxidative injury. Catechins are also associated with anti-inflammatory and cardio protective effects, contributing significantly to the pharmacological potential of sea buckthorn leaves¹⁵.

Tannins and Galloyl Derivatives: The leaves of *H. salicifolia* contain tannins and galloyl derivatives such as pedunculagin and dimethyl galloyl hexoside. Tannins possess strong antioxidant activity because of their efficient hydrogen donating capacity to neutralize free radicals. These phytoconstituents help preserve

membrane integrity, minimize oxidative injury, and improve cellular resistance during pathological conditions¹³.

The pharmacological significance of *H. salicifolia* leaves can be attributed to the combined action of flavonoids, phenolic acids, tannins, and other polyphenols. These compounds collectively target multiple biochemical pathways involved in oxidative stress, inflammation, cellular injury, and metabolic dysfunction. Such a multi-targeted mechanism may explain the traditional and experimentally reported therapeutic benefits of *H. salicifolia*, including antioxidant, adaptogenic, and stress-protective effects^{12, 14, 15}.

TABLE 1: PHYTOCONSTITUENTS OF *H. SALICIFOLIA* LEAVES

Phytochemical	Major Constituents
Flavonoids & Flavonols	Quercetin, Isorhamnetin, Kaempferol-3-O-rhamnoside, Dihexosylisorhamnetin, 6-Hydroxyluteolin-7-rhamnoside
Flavones & Flavone Glycosides	Apigenin 4'-O-rhamnoside, Apigenin 6,8-di-C-glucoside, Neodiosmin
Isoflavones	3'-Hydroxygenistein
Flavanols (Catechin Derivatives)	Epigallocatechin-3-O-gallate (EGCG), Methylgalloyl epicatechin, 3'-O-methylcatechin
Phenolic Acids	Chlorogenic acid, Quinic acid, 3-p-Coumaroylquinic acid, Caffeoyl-2-hydroxyethane-1,1,2-tricarboxylic acid
Galloyl Esters	Dimethyl galloyl hexoside
Tannins	Pedunculagin
Polymethoxyflavones	3-Methoxysinensetin
Other Phenolic Compounds	Glucaric acid, 2,3-Dihydroxy-1-guaiacylpropanone

Source: Das M *et al.* 2026¹⁵

Pharmacological Activities: The leaves of *Hippophae salicifolia* possess diverse pharmacological activities owing to the presence of flavonoids, phenolic acids, flavonols, tannins and other polyphenolic compounds. These bioactive constituents contribute to antioxidant, anti inflammatory, adaptogenic and stress revealing activities that contribute to medical value of plant^{11, 15}.

Antioxidant Activity: *H. salicifolia* leaf extracts demonstrate strong antioxidant potential. Due to the presence of quercetin, isorhamnetin, chlorogenic acid, kaempferol derivatives, and apigenin derivatives. These phytochemicals neutralizere active oxygen species, reduce oxidative damage, and strengthen endogenous antioxidant defense mechanisms, thereby maintaining cellular redox balance^{12, 15}.

Anti-inflammatory Activity: Polyphenols and flavonoids present in the leaves regulate

inflammatory signaling pathways and suppress the synthesis and release pro inflammatory mediators. This activity may help protect tissues from inflammation-induced damage^{11, 15}.

Neuroprotective Activity: Flavonoids, Catechins and phenolic acids exhibit neuroprotective effects by lowering oxidative burden and protecting neuronal cells against oxidative injury¹⁴⁻¹⁵.

Adaptogenic and Anti-stress Activity: The leaves are rich in antioxidant phytochemicals that help improve cellular resistance against environmental and physiological stress. This adaptogenic effect may contribute to protection against stress-induced disorders¹⁴.

Synergistic Multi-target Effects: The overall pharmacological activity of *Hippophae salicifolia* leaves is a result of the combined action of multiple bioactive compounds. These compounds work together to produce a broad protective effect

against stress-induced damage, making them effective in targeting multiple aspects of neuropsychiatric disorders^{11, 12, 14, 15}.

Overall, *Hippophae salicifolia* leaves exhibit multiple pharmacological activities that contribute to protection against stress-induced neuronal dysfunction. Their combined effects on oxidative stress, inflammation, neuronal health highlight their potential role in managing anxiety-related conditions.

Mechanism of Action of Major Phytochemicals

Flavonoids: Flavonoids are one of the main group of phytochemicals founds in *H. salicifolia* leaves. These include derivatives of quercetin, kaempferol, isorhamnetin, apigenin and luteolin. Experimental studies show that some flavonoids such as apigenin can bind to the same site on GABA_A receptors where benzodiazepines work. However, *H. salicifolia* contains apigenin derivatives rather than free apigenin. These compounds may contribute to similar pharmacological effects¹⁵⁻¹⁶, Quercetin has been found to reduce behavior changes caused by long term unpredictable stress. It does this by lowering oxidative damage and reducing inflammation in the hippocampus^{15, 17}. Together, these effects on GABAergic signaling, oxidative stress and neuroinflammation may explain why flavonoids-rich extract of *H. salicifolia* could help with anxiety and protect nerve cells.

Catechins: Catechin derivatives, especially EGCG work mainly through antioxidant pathways. Studies report that EGCG can switch on the keep1/Nrf2 signaling pathway. This leads to higher production of the body's own antioxidant enzymes and lowers the level of reactive oxygen species inside cells and protects nerve cells from oxidative damage. Because of this, EGCG helps to keep the cells redox balance stables and may reduce brain cell damage caused by long term stress¹⁸.

Phenolic Acids: Phenolic acids, especially chlorogenic acid are known for their antioxidant effects and help to control the cellular redox balance. Research shows that chlorogenic acid activates the Nrf2-ARE pathway and also directly cleanup the reactive oxygen species. When this pathway is activated, the cells' antioxidant defense gets stronger and oxidative damage to nerve tissue

is reduced. In this way, phenolic acids may help to protect brain function during long period of oxidative stress¹⁹.

Tannins: Hydrolysable tannins such as pedunculagin have strong antioxidant and anti-inflammatory effects. Evidence suggests they can neutralize ROS, block lipid peroxidation and calm down inflammatory processes. This protects cells from oxidative injury. While there isn't much direct proof yet that they reduce anxiety, their ability to lower the oxidative stress and inflammation may still help to keep neuron healthy under stress related conditions²⁰.

Relevance to Anxiety Disorders: There isn't just one reason behind anxiety disorders. They usually develop when hormone balance, oxidative stress, inflammation, and brain chemicals all get disturbed together. Disturbances in the hypothalamic pituitary adrenal (HPA) axis, increased oxidative stress, and elevated inflammatory mediators collectively contribute to neuronal dysfunction and behavioral abnormalities^{2, 7}.

Anxiety disorders are frequently linked to oxidative imbalance neuroinflammation, and neuronal dysfunction. Recent phytochemical investigations of *Hippophae salicifolia* leaves have revealed the presence of several bioactive compounds including quercetin, isorhamnetin, kaempferol derivatives, chlorogenic acid, apigenin derivatives, and other polyphenolic constituents. These compounds are known as antioxidants and brain protectors. That may help reduce oxidative damage and maintain neuronal function^{11, 12, 14, 15}.

Animal studies have also shown that *H. salicifolia* leaf extracts can protect against stress and act as Adaptogens during long-term stress. Since oxidative stress and prolonged stress exposure are important factors involved in the initiation and advancement of anxiety disorders, the phytochemical composition and stress-modulating properties of *H. salicifolia* suggest its potential relevance in anxiety management^{12, 14, 15}.

But direct studies evaluating the anxiolytic activity of *H. salicifolia* leaves are limited, the available evidence provides a scientific rationale for further investigation of its therapeutic significance in

anxiety and other stress related neuropsychiatric disorders.

DISCUSSION: *Hippophae salicifolia* leaves have gained attention for both their chemistry and medicinal potential. Work so far shows the leaves are rich in flavonoids, flavonols, phenolic acids, flavanols and tannins. These phytochemicals contribute to the pharmacological potential of *H. salicifolia* leaves^{13, 15}.

A big reason for this interest is the plant's antioxidant capacity. The phytochemicals in it can reduce reactive oxygen species, decrease oxidative damage, and keep cells from getting injured¹³. There's also evidence that *H. salicifolia* helps the body cope with long-term stress. It appears to have adaptogenic and stress-protective properties that may help restore balance when stress goes on for a long time¹⁴.

Since oxidative stress plays a part in anxiety, these compounds could potentially protect nerve cells. But we don't have many direct studies yet on whether *H. salicifolia* leaves actually work as an anxiolytic. However additional well designed experimental studies are required to establish the anxiolytic potential of *H. salicifolia*¹⁴⁻¹⁵.

Taken together, the data suggest *H. salicifolia* leaves contain useful bioactive compounds. Their antioxidant and stress-buffering effects make them a candidate worth exploring for anxiety and other stress-related problems^{11, 15}.

Research GAP: *Hippophae salicifolia* has been getting more attention from researchers, but lots of things still unknown. Most studies till now have focused on what's inside the leaves, like its chemicals, antioxidant capacity, germ-fighting ability, blood sugar effects, and stress-buffering properties. When it comes to anxiety, not much work has been done^{13, 15}.

The bigger problem is that we're missing proper animal studies. Standard tests used for anxiety such as the Elevated Plus Maze²¹, Open Field Test²², Light Dark Box²³, and Hole Board Test²⁴, have barely been applied to *H. salicifolia* leaf extracts. Without that data, we can't really say if it helps with anxiety²⁵. Current understanding of the neurochemical mechanisms responsible for its

possible anxiolytic activity is also incomplete. We know the leaves contain flavonoids, phenolic acids and other antioxidants. But we don't know yet how these compounds interact with the brain signals involved in anxiety. There are other missing pieces as well. The right dose hasn't been worked out. We don't know how it moves through the body. And there's no information yet on long-term safety or whether it actually works in humans. Therefore, additional preclinical investigations followed by well designed clinical studies are necessary to determine the therapeutic value of *H. salicifolia* as a natural investigation for anxiety disorders.

Future Perspectives: In future researchers should properly test if *H. salicifolia* leaves can reduce anxiety. This means running standard animal tests like the Elevated Plus Maze, Open Field Test, Light Dark Box and similar models. That kind of data will give us a clearer answer about whether it actually helps with anxiety disorders.

We also need to figure out which compounds in the plant are doing the work. Once we know that, we can understand better how they protect nerve cells and help the body handle stress. Other important things to check are the right dose, how the body absorbs and removes it, safety in short-term use, and any problems from using it for a long time. In the end, human trials will be needed. Only then can we confirm if *H. salicifolia* can be used as a plant-based option for managing anxiety.

CONCLUSION: *Hippophae salicifolia* leaves have a lot of active plant compounds. They contain flavonoids, phenolic acids, tannins and other polyphenols. Together, these compounds can fight oxidation, help the body manage stress, and support brain cell health. Because of this, the plant looks useful from a medical point of view. Early data also suggests they may lower oxidative damage and help keep the nerve function normally. We don't have direct proof, yet that *H. salicifolia* works for anxiety. But based on what's in the leaves and what we know about its effects, it seems like a good candidate to study further for anxiety-related problems. More lab work and human studies are needed now. That's the only way to confirm if it's safe, if it actually works, and if it can be used as a treatment.

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