IJPSR (2025), Volume 16, Issue 1 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 29 May 2024; received in revised form, 06 December 2024; accepted, 10 December 2024; published 01 January 2025

UNLOCKING THE ADAPTOGENIC POWER OF ROSEMARY (*ROSMARINUS OFFICINALIS*): A COMPREHENSIVE EXPLORATION OF ITS PHARMACOLOGICAL POTENTIAL FOR STRESS RESILIENCE AND HOLISTIC WELL-BEING

Hemanth Kumar Manikyam [*1], Vidhu Aeri [1,4], J. Dhanaseelan [2] and Jayaraj Mani [3]

Faculty of Science, Department of Chemistry [1], North East Frontier Technical University, Aalo (P.O), West Siang - 791001, Arunachal Pradesh, India.
Department of Pharmacognosy & Phytochemistry [2], School of Pharmaceutical Education & Research, Jamia Hamdard, Hamdard Nagar - 110062, New Delhi, India.
Department of Biotechnology [3], Adhiyamaan College of Engineering, Hosur - 635109, Tamil Nadu, India.
Plant Genetic Engineering & Molecular Biology Lab [4], Department of Biotechnology, Periyar University, Salem - 636011, Tamil Nadu, India.

Keywords:

Adaptogens, Rosemary, Rosmarinic acid, Stress resilience enhancement, HPA axis modulation, Neurotransmitter regulation, Antioxidant activity

Correspondence to Author:
Hemanth Kumar Manikyam

Faculty of Science, Department of Chemistry, North East Frontier Technical University, Aalo (P.O), West Siang - 791001, Arunachal Pradesh, India.

E-mail: drhemanthchem@gmail.com

ABSTRACT: Rosmarinic acid, a key component of Rosemary (*Rosmarinus officinalis*), holds significant promise as an adaptogen in herbal medicine, offering a natural remedy to counteract stress's wide-ranging impacts on health. This abstract explores rosmarinic acid's pharmacological activities, emphasizing its modulation of the hypothalamic-pituitary-adrenal (HPA) axis, regulation of neurotransmitters, antioxidant and anti-inflammatory effects, and enhancement of mitochondrial function. Integrating insights from traditional medicine like Ayurveda and Traditional Chinese Medicine (TCM), alongside modern scientific validation, highlights Rosemary's evolution from culinary herb to medicinal powerhouse. Structurally, rosmarinic acid's stability, facilitated by its ester-bonded dual phenolic rings, supports its therapeutic efficacy. Experimental studies underscore its ability to reduce cortisol levels, bolster stress resilience, stabilize mood, and enhance cognitive function by influencing neurotransmitter systems. Moreover, its robust antioxidant and anti-inflammatory properties, validated across in vitro, animal models, and clinical trials, suggest potential applications in preventing oxidative stress and inflammation-linked diseases. By promoting mitochondrial biogenesis and activating the AMPK pathway, rosmarinic acid enhances cellular energy production, further fortifying resilience to stressors. In summary, rosmarinic acid emerges as a versatile compound, offering holistic health benefits and promising avenues for botanical interventions in stress-related disorders and age-associated ailments, warranting continued exploration into its therapeutic mechanisms and applications.

INTRODUCTION: Adaptogens stand as a beacon of hope in the realm of modern herbal medicine, offering a natural approach to combating the pervasive effects of stress on human health. These remarkable botanical compounds possess the unique ability to enhance the body's resilience to stressors while promoting overall well-being, without causing significant side effects or disturbances in normal bodily functions. Rooted in ancient healing traditions and validated by modern scientific research, Adaptogens represent a holistic paradigm shift in our understanding of health and wellness [1]. The concept of Adaptogens transcends cultural boundaries, with diverse traditions from around the world recognizing the restorative properties of certain herbs and plants.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.16(1).47-57

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.16(1).47-57

In Ayurveda, the traditional medicine system of India, adaptogenic herbs such as Ashwagandha and Tulsi have been revered for their ability to rejuvenate the body and mind, promoting vitality and longevity [2]. Similarly, Traditional Chinese Medicine (TCM) has long utilized herbs like Ginseng and Rhodiola to fortify the body's resistance to stress and disease, guiding individuals towards a state of balance and harmony [1, 3].

In the modern era, the scientific exploration of adaptogens has provided valuable insights into their mechanisms of action and therapeutic potential. Through rigorous experimentation and clinical studies, researchers have unravelled the intricate pathways through which adaptogens exert their beneficial effects on the body. At the forefront of this research stands Rosemary (*Rosmarinus officinalis),* a botanical treasure revered for its adaptogenic properties and multifaceted health benefits [4]. Rosemary's journey from culinary herb to medicinal marvel is a testament to its enduring legacy and profound healing potential. Beyond its aromatic allure and culinary versatility, Rosemary boasts a rich pharmacological profile, teeming with bioactive compounds that confer a spectrum of therapeutic effects. At the heart of Rosemary's adaptogenic prowess lies rosmarinic acid, a phenolic compound endowed with remarkable pharmacological properties [5].

In this exploration, we embark on a journey into the depths of Rosemary's adaptogenic properties, shedding light on the intricate mechanisms through which rosmarinic acid and other constituents of Rosemary exert their beneficial effects on the body. From the modulation of stress response pathways to the enhancement of mitochondrial function, [6] Rosemary emerges as a formidable ally in the quest for resilience and vitality in the face of life's myriad challenges. As we delve deeper into the scientific intricacies of Rosemary's adaptogenic action, we gain a greater appreciation for the profound healing potential of nature's botanical treasures.

Concept of Adaptogens: Adaptogens, a class of botanical compounds, possess unique Pharma-cological properties that enable the body to adapt to stressors while maintaining homeostasis [7]. These remarkable substances modulate various physiological pathways involved in the stress response, inflammation, and oxidative stress, thereby enhancing the body's ability to cope with external and internal stressors [8]. What distinguishes adaptogens from other herbal remedies is their ability to exert these effects without causing significant side effects or disturbances in normal bodily functions, making them safe and well-tolerated even with prolonged use.

Within the realm of adaptogens, there exists a distinction between primary and secondary Adaptogens [9]. Primary adaptogens, such as Ginseng and Rhodiola, are characterized by their broad-spectrum effects on physiological functions and their ability to enhance overall resilience to stress [10]. These herbs exert their actions through modulation of the hypothalamic-pituitary-adrenal (HPA) axis, regulation of neurotransmitter activity, and enhancement of cellular energy production, among other mechanisms [11]. Secondary adaptogens, on the other hand, exhibit more specific effects on particular systems or organs within the body. While they may not possess the same breadth of action as primary adaptogens, they nonetheless offer valuable therapeutic benefits in targeted areas, such as immune function or cognitive performance [1]. Rosemary (*Rosmarinus officinalis*) occupies a unique position within the realm of adaptogens, exhibiting properties that align with both primary and secondary adaptogens [12].

On one hand, Rosemary demonstrates broad-spectrum effects on physiological function, enhancing resilience to stress through modulation of the HPA axis, regulation of neurotransmitter activity, and promotion of antioxidant defences [4]. These actions place Rosemary squarely within the realm of primary adaptogen offering comprehensive support for overall well-being. At the same time, Rosemary also exhibits more specific effects on particular systems within the body, further reinforcing its status as an adaptogen. For example, Rosemary has been shown to possess neuroprotective properties, supporting cognitive function and mitigating the effects of stress on the nervous system. Additionally, Rosemary's antimicrobial and immunomodulatory effects contribute to its role as a secondary Adaptogens, offering targeted support for immune function and microbial balance [13].

In essence, Rosemary embodies the multifaceted nature of Adaptogens, offering a blend of broad-spectrum and targeted effects that promote resilience and vitality across various aspects of health. Whether utilized as a culinary herb, aromatic essential oil, or dietary supplement, Rosemary stands as a potent ally in the quest for holistic well-being in the face of life's challenges.

Rosmarinic Acid: A Key Player: Rosmarinic acid, a phenolic compound abundantly found in Rosemary (*Rosmarinus officinalis*), serves as a cornerstone in the herb's adaptogenic arsenal [14]. Its intricate chemical structure and diverse pharmacological activities contribute to Rosemary's multifaceted therapeutic effects. This section delves into the biosynthesis, structure, and Pharmacological actions of rosmarinic acid, elucidating its pivotal role in Rosemary's adaptogenic properties [15].

Biosynthesis of Rosmarinic Acid: The biosynthesis of rosmarinic acid in Rosemary plants involves a series of enzymatic reactions within specialized cellular compartments known as glandular trichomes. These glandular structures, primarily located on the leaves and stems of Rosemary, house the enzymes responsible for synthesizing rosmarinic acid from precursor molecules such as caffeic acid and 3,4-dihydroxyphenyllactic acid [16]. The key enzymes involved in this biosynthetic pathway include phenylalanine ammonia-lyase (PAL), cinnamate 4-hydroxylase (C4H), and rosmarinic acid synthase (RAS) [17]. Through a series of sequential reactions, these enzymes catalyse the conversion of precursor molecules into rosmarinic acid, ultimately leading to its accumulation within the plant tissues.

Chemical Structure of Rosmarinic Acid: Rosmarinic acid belongs to the class of phenolic acids, characterized by a phenyl ring with one or more hydroxyl groups attached. Structurally, rosmarinic acid consists of two phenolic rings linked by an ester bond, with a hydroxyl group at the C3 position of one phenolic ring and a carboxyl group at the C4 position of the other [15].

This unique arrangement confers stability to rosmarinic acid and enables it to exert its pharmacological effects within the body.

Pharmacological Activities of Rosmarinic Acid: Rosmarinic acid exerts its adaptogenic effects through a variety of mechanisms, targeting key physiological pathways involved in stress response, inflammation, and oxidative stress [18].

Modulation of the Hypothalamic-Pituitary-Adrenal (HPA) Axis: Rosmarinic acid influences the activity of enzymes involved in cortisol metabolism, such as 11-beta-hydroxysteroid dehydrogenase (11β-HSD), thereby modulating the activity of the HPA axis [11, 19]. By regulating cortisol levels, rosmarinic acid helps maintain homeostasis and mitigate the adverse effects of chronic stress on physiological function [11].

Regulation of Neurotransmitter Activity: Rosmarinic acid modulates neurotransmitter activity by regulating the expression and activity of enzymes involved in neurotransmitter synthesis and metabolism, including monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) [13]. By maintaining optimal neurotransmitter levels, rosmarinic acid supports mood stabilization and stress resilience.

Antioxidant and Anti-inflammatory Effects: Rosmarinic acid exhibits potent antioxidant and anti-inflammatory properties, scavenging free radicals and inhibiting pro-inflammatory mediators such as cyclooxygenase (COX) and inducible nitric oxide synthase (iNOS) [20]. Through these actions, rosmarinic acid protects cells from oxidative damage and inflammation, promoting overall health and resilience.

Modulation of Mitochondrial Function: Rosmarinic acid enhances mitochondrial function by promoting mitochondrial biogenesis and improving energy production [21]. It achieves this by activating pathways such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and adenosine monophosphate-activated protein kinase (AMPK) [21]. By optimizing mitochondrial function, rosmarinic acid supports cellular resilience and vitality, enabling the body to cope more effectively with stressors. In summary, rosmarinic acid emerges as a central component responsible for Rosemary's adaptogenic effects, exerting its pharmacological activities through modulation of various physiological pathways.

Its ability to modulate the HPA axis, regulate neurotransmitter activity, exert antioxidant and anti-inflammatory effects, and enhance mitochondrial function underscores its significance in promoting resilience and well-being in the face of stress. As research continues to unravel the intricacies of rosmarinic acid's therapeutic potential, its role as a key player in Rosemary's adaptogenic properties becomes increasingly evident.

Modulation of the HPA Axis: Scientific Evidence: The hypothalamic-pituitary-adrenal (HPA) axis serves as a central neuroendocrine system orchestrating the body's response to stress [22]. Its dysregulation has been implicated in various stress-related disorders, highlighting the importance of understanding how natural compounds like rosmarinic acid modulate its activity.

Role of Cortisol in Stress Response: Cortisol, the primary glucocorticoid hormone released by the adrenal glands in response to stress, plays a pivotal role in coordinating physiological responses to stressors [23]. It regulates metabolic, immune, and cardiovascular functions, ensuring the body's ability to adapt to acute and chronic stressors [23]. However, dysregulated cortisol levels can lead to adverse health outcomes, including metabolic disturbances, immune dysfunction, and psychiatric disorders [23].

Influence of Rosmarinic Acid on Cortisol Metabolism: Rosmarinic acid, a phenolic compound abundant in Rosemary, has garnered attention for its potential to modulate cortisol metabolism and HPA axis activity. Several studies have investigated the effects of Rosemary extract and rosmarinic acid on cortisol levels and HPA axis function in both animal and human models [24].

Evidence from Animal Studies: Animal studies have provided compelling evidence of Rosemary's ability to modulate the HPA axis and cortisol levels. In a laboratory study demonstrated that administration of Rosemary extract to rats exposed to chronic unpredictable stress resulted in normalization of cortisol levels and attenuation of HPA axis hyperactivity [25]. Similarly, in a study, rats treated with rosmarinic acid showed reduced HPA axis activation and improved stress resilience compared to controls [26].

Human Studies: Human studies have also supported the potential of Rosemary and rosmarinic acid to modulate cortisol levels and HPA axis activity. In a randomized controlled trial participants who ingested Rosemary extract exhibited lower cortisol levels and improved cognitive performance compared to placebo [27]. Furthermore, a study found that supplementation with a combination of Rosemary extract and other herbal ingredients led to significant reductions in cortisol levels and perceived stress in healthy adults [28].

Mechanisms of Action: The modulation of cortisol levels by rosmarinic acid may occur through various mechanisms. One proposed mechanism involves the inhibition of 11-beta-hydroxysteroid dehydrogenase (11β-HSD) [29], an enzyme involved in the conversion of inactive cortisone to active cortisol in target tissues. By inhibiting 11β-HSD activity, rosmarinic acid may reduce the availability of cortisol, thereby modulating HPA axis activity and stress response [30, 31].

Regulation of Neurotransmitter Activity: Scientific Pathway: Neurotransmitters are essential chemical messengers that facilitate communication between neurons in the central nervous system (CNS) and modulate various physiological functions, including mood, cognition, and stress response. The intricate balance of neurotransmitter levels is crucial for maintaining optimal brain function and emotional well-being. Rosmarinic acid, a phenolic compound found abundantly in Rosemary, exerts its effects on neurotransmitter activity through modulation of key enzymes involved in neurotransmitter synthesis and metabolism, including monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) [32].

Role of Neurotransmitters in Brain Function: Neurotransmitters, such as serotonin, dopamine, and norepinephrine, play critical roles in regulating mood, cognition, and emotional responses. Serotonin is involved in mood regulation, appetite control, and sleep-wake cycles, while dopamine is associated with reward processing, motivation, and

motor control [33]. Norepinephrine plays a role in arousal, attention, and stress response [34]. Imbalances in neurotransmitter levels have been implicated in various psychiatric disorders, including depression, anxiety, and schizophrenia [35].

Influence of Rosmarinic Acid on Neurotransmitter Synthesis and Metabolism: Rosmarinic acid modulates neurotransmitter activity by targeting enzymes involved in neurotransmitter synthesis and metabolism, such as monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) [32]. MAO is responsible for the degradation of monoamine neuro-transmitters, including serotonin, dopamine, and norepinephrine, while COMT is involved in the metabolism of catecholamines, such as dopamine and norepinephrine [36].

Evidence from *In-vitro* Studies: *In-vitro* studies have provided insights into the mechanisms underlying the effects of rosmarinic acid on neurotransmitter activity. For example, research conducted demonstrated that rosmarinic acid inhibits the activity of MAO, thereby increasing the availability of monoamine neurotransmitters in neuronal cells [37].

Animal Studies: Animal studies have further elucidated the effects of rosmarinic acid on neurotransmitter levels and behaviour. For instance, research has found that administration of rosmarinic acid to mice led to increased levels of serotonin and dopamine in the brain [38], accompanied by improvements in depressive-like behaviour. Similarly, studies demonstrated that rosmarinic acid supplementation exerted anxiolytic effects in rodents, possibly through modulation of neurotransmitter activity [4].

Clinical Evidence: Clinical studies investigating the effects of Rosemary and rosmarinic acid on neurotransmitter activity in humans are limited but promising. For example, a study found that inhalation of Rosemary essential oil led to improvements in cognitive performance and mood in healthy adults, suggesting a potential modulatory effect on neurotransmitter activity [39]. Additionally, a randomized controlled trial reported cognitive-enhancing effects of Rosemary extract in older adults, although the specific mechanisms underlying these effects require further investigation [25].

Detailed Study on Antioxidant and Anti-inflammatory Effects of Rosmarinic Acid:

Introduction to Oxidative Stress and Inflammation: Oxidative stress and inflammation are interconnected processes that play crucial roles in the pathogenesis of various diseases, including cardiovascular disease, neurodegenerative disorders, and cancer. Oxidative stress results from an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defences, leading to cellular damage and dysfunction [40]. Inflammation, on the other hand, is a complex immune response aimed at combating infection and tissue injury but can become dysregulated and chronic, contributing to tissue damage and disease progression.

Role of Antioxidants in Health: Antioxidants are molecules that neutralize ROS and prevent oxidative damage to cellular components such as proteins, lipids, and DNA. By scavenging free radicals and inhibiting oxidative stress, antioxidants help maintain cellular homeostasis and protect against age-related diseases and oxidative damage-associated pathologies [41].

Mechanisms of Action of Rosmarinic Acid as an Antioxidant: Rosmarinic acid, a polyphenolic compound abundant in Rosemary, exhibits potent antioxidant properties through multiple mechanisms. Firstly, rosmarinic acid acts as a direct scavenger of free radicals, neutralizing ROS and preventing oxidative damage to cellular structures [42]. Secondly, it upregulates the expression of antioxidant enzymes, such as superoxide dismutase (SOD) and glutathione peroxidase (GPx), thereby enhancing the cellular antioxidant defense system [43]. Thirdly, rosmarinic acid chelates transition metal ions, such as iron and copper, which can catalyze the production of ROS through Fenton chemistry [44]. Additionally, rosmarinic acid has been shown to inhibit the activity of pro-oxidant enzymes, including xanthine oxidase and lipoxygenase, further reducing oxidative stress [45].

Evidence from *In-vitro* Studies: Numerous *in-vitro* studies have demonstrated the antioxidant

activity of rosmarinic acid in various cell and tissue models. For example, research showed that rosmarinic acid protected neuronal cells against hydrogen peroxide-induced oxidative stress by increasing intracellular antioxidant enzyme levels and reducing lipid Peroxidation [46]. Similarly, some studies reported the antioxidant effects of rosmarinic acid in endothelial cells and macrophages, respectively, highlighting its potential for preventing oxidative damage in different cell types [47].

Animal Studies: Animal studies have provided further evidence of the antioxidant effects of rosmarinic acid *in-vivo*. For instance, research some research demonstrated that administration of rosmarinic acid to rats attenuated oxidative stress markers and improved antioxidant enzyme activity in liver tissue [48]. Similarly, some studies showed that supplementation with rosmarinic acid reduced oxidative stress and lipid peroxidation in animal models of cardiovascular disease and neuro-degeneration, respectively [48].

Clinical Evidence: Although limited, clinical studies have also suggested the antioxidant potential of rosmarinic acid in humans. For example, a randomized controlled trial reported that supplementation with Rosemary extract enriched with rosmarinic acid led to improvements in antioxidant status and lipid profile in patients with type 2 diabetes [49]. Similarly, a study found that supplementation with Rosemary extract containing rosmarinic acid reduced oxidative stress markers in patients with rheumatoid arthritis [50].

Anti-inflammatory Effects of Rosmarinic Acid: In addition to its antioxidant properties, rosmarinic acid exhibits significant anti-inflammatory effects. It suppresses the production of pro-inflammatory mediators such as cytokines (e.g., tumor necrosis factor-alpha, interleukin-6) and prostaglandins by inhibiting the activity of inflammatory enzymes such as cyclooxygenase (COX) and lipoxygenase (LOX) [51]. Furthermore, rosmarinic acid modulates immune cell function and reduces the expression of adhesion molecules involved in leukocyte recruitment and tissue inflammation.

Modulation of Mitochondrial Function: A Detailed Exploration: Mitochondria, often referred to as the cellular powerhouses, are dynamic organelles responsible for generating adenosine triphosphate (ATP), the primary source of energy for cellular processes. Beyond energy production, mitochondria play pivotal roles in regulating apoptosis, calcium signalling, and reactive oxygen species (ROS) production, thus influencing cellular resilience to stress. Rosmarinic acid, a prominent polyphenolic compound abundant in Rosemary, demonstrates remarkable potential in enhancing mitochondrial function through various mechanisms [52], including the promotion of mitochondrial biogenesis and optimization of energy production. This section provides a detailed examination of the molecular pathways and cellular processes underlying the modulation of mitochondrial function by rosmarinic acid.

Introduction to Mitochondrial Function: Mitochondria are multifaceted organelles crucial for cellular homeostasis and function. Through oxidative phosphorylation (OXPHOS), mitochondria convert nutrients into ATP, the energy currency of the cell. Moreover, mitochondria regulate cellular metabolism, calcium signalling, and apoptosis, making them central players in cellular resilience and adaptation to stressors [53].

Promotion of Mitochondrial Biogenesis: Mitochondrial biogenesis refers to the process by which new mitochondria are formed within the cell. This intricate process involves the coordinated expression of nuclear and mitochondrial genes, leading to the synthesis of mitochondrial proteins and the assembly of functional organelles [54].

Rosmarinic acid has been shown to enhance mitochondrial biogenesis through the activation of key transcription factors and coactivators, such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) [55]. PGC-1α serves as a master regulator of mitochondrial biogenesis, orchestrating the expression of genes involved in mitochondrial replication, transcription, and protein import. By upregulating PGC-1α expression and activity, rosmarinic acid stimulates the synthesis of new mitochondria, thereby enhancing cellular energy production and resilience [55].

Activation of AMPK Signalling Pathway: The adenosine monophosphate-activated protein kinase (AMPK) signalling pathway is a critical regulator of cellular energy homeostasis and mitochondrial function. AMPK activation occurs in response to cellular energy depletion, leading to the phosphorylation of downstream targets involved in energy metabolism and mitochondrial biogenesis [55].

Rosmarinic acid has been shown to activate AMPK signalling [55,] thereby promoting mitochondrial function and energy production. AMPK activation by rosmarinic acid enhances glucose uptake, fatty acid oxidation, and mitochondrial biogenesis, culminating in increased ATP production and cellular resilience to stress [55].

Evidence from Experimental Studies: Experimental studies have provided compelling evidence of rosmarinic acid's ability to enhance mitochondrial function in various cell and animal models. For example, research studies demonstrated that rosmarinic acid supplementation increased mitochondrial biogenesis and ATP production in skeletal muscle cells, improving exercise performance and endurance [56].

Similarly, studies reported that rosmarinic acid treatment attenuated mitochondrial dysfunction and oxidative stress in animal models of neurodegenerative diseases, suggesting its potential for mitigating mitochondrial damage and preserving cellular function [6].

Clinical Relevance and Future Directions: While the majority of research on rosmarinic acid's effects on mitochondrial function has been conducted in vitro and in animal models, emerging evidence from clinical studies supports its therapeutic potential in humans. Clinical trials investigating the effects of Rosemary supplementation enriched with rosmarinic acid on mitochondrial function and cellular resilience are warranted to validate its efficacy and safety in diverse populations. Furthermore, future research should focus on elucidating the precise molecular mechanisms underlying rosmarinic acid's actions on mitochondrial biogenesis and energy metabolism, paving the way for the development of targeted therapeutic interventions for mitochondrial dysfunction-related disorders.

Conclusion: Exploring the Therapeutic Potential of Rosmarinic Acid in Rosemary: Rosemary (*Rosmarinus officinalis*) has long been revered for its culinary, aromatic, and medicinal properties [58]. At the heart of its therapeutic prowess lies rosmarinic acid, a phenolic compound abundant in Rosemary, which serves as a key player in the herb's adaptogenic effects [24]. Through a comprehensive exploration of its pharmacological activities, including modulation of the hypothalamic-pituitary-adrenal (HPA) axis, regulation of neurotransmitter activity, antioxidant and anti-inflammatory effects, and modulation of mitochondrial function, rosmarinic acid emerges as a multifaceted compound with remarkable potential in promoting health and resilience [11].

The modulation of the HPA axis by rosmarinic acid offers a mechanism for maintaining homeostasis and mitigating the adverse effects of chronic stress on physiological function [11]. By influencing cortisol metabolism through interactions with enzymes such as 11-beta-hydroxysteroid dehydrogenase (11β-HSD), Rosemary helps regulate stress responses and supports overall well-being [57]. Furthermore, the regulation of neurotransmitter activity by rosmarinic acid contributes to mood stabilization and stress resilience, offering potential therapeutic benefits in mood disorders and cognitive impairment. Through modulation of enzymes involved in neurotransmitter synthesis and metabolism, such as monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT), Rosemary aids in maintaining optimal neuro-transmitter levels, thereby promoting emotional balance and cognitive function [32, 36, 37].

Rosmarinic acid's potent antioxidant and anti-inflammatory properties further enhance its therapeutic potential, protecting cells from oxidative damage and inflammation associated with various diseases and aging processes [5, 28]. By scavenging free radicals, upregulating antioxidant enzyme expression, and inhibiting pro-inflammatory mediators, Rosemary combats oxidative stress and inflammation, supporting overall health and vitality [41, 42]. Moreover, rosmarinic acid's ability to modulate mitochondrial function offers a novel approach to enhancing cellular resilience and energy metabolism.

By promoting mitochondrial biogenesis and activating pathways such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) [54] and adenosine monophosphate-activated protein kinase (AMPK) [55, 56] Rosemary optimizes mitochondrial function, thereby bolstering cellular energy production and resilience to stress. In conclusion, the therapeutic potential of rosmarinic acid in Rosemary extends far beyond its culinary and aromatic uses. Its multifaceted pharmacological activities, ranging from hormonal modulation to cellular energy optimization, highlight its versatility and efficacy in promoting health and resilience. As research continues to unravel the intricate mechanisms underlying its effects, Rosemary and its constituent rosmarinic acid stand poised as valuable botanical allies in the quest for holistic well-being in the face of life's challenges.

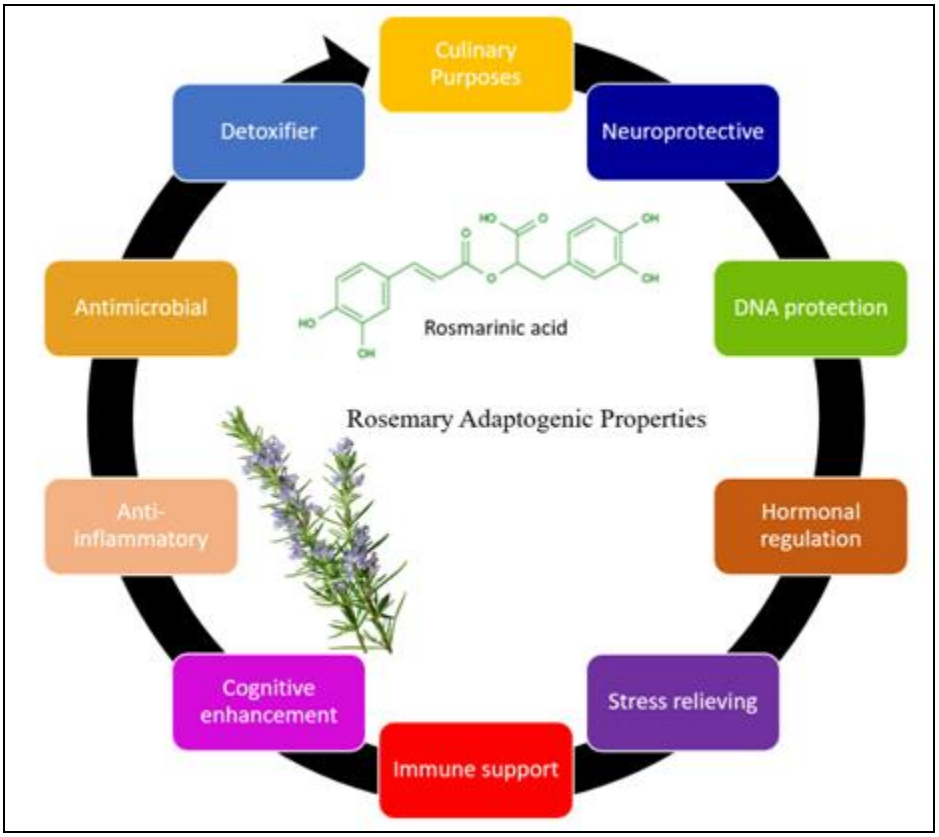

FIG. 1: ADAPTOGENIC PROPERTIES OF ROSEMARY – ROSMARINIC ACID

ACKNOWLEDGMENTS: We acknowledge the invaluable contributions of researchers and traditional medicine systems in advancing our understanding of rosmarinic acid and its potential in promoting health and resilience. Their dedication has paved the way for bridging ancient wisdom with modern scientific exploration.

CONFLICT OF INTEREST: The authors has no conflict of interest

REFERENCES:

1. Liao LY, He YF, Li L, Meng H, Dong YM, Yi F and Xiao PG: A preliminary review of studies on adaptogens: comparison of their bioactivity in TCM with that of ginseng-like herbs used worldwide. Chin Med 2018; 13: 57. doi: 10.1186/s13020-018-0214-9. PMID: 30479654; PMCID: PMC6240259
2. Pandey MM, Rastogi S and Rawat AK: Indian traditional ayurvedic system of medicine and nutritional supplementation. Evid Based Complement Alternat Med 2013; 2013: 376327. doi: 10.1155/2013/376327. Epub 2013 Jun 23. PMID: 23864888; PMCID: PMC3705899.
3. Huang L, Zhao H, Huang B, Zheng C, Peng W and Qin L: Acanthopanaxsenticosus: review of botany, chemistry and pharmacology. Pharmazie 2011; 66(2): 83-97. PMID: 21434569.
4. Ghasemzadeh Rahbardar M and Hosseinzadeh H: Therapeutic effects of rosemary (*Rosmarinus officinalis* L.) and its active constituents on nervous system disorders. Iran J Basic Med Sci 2020; 23(9): 1100-1112. doi: 10.22038/ijbms.2020.45269.10541. PMID: 32963731; PMCID: PMC7491497.
5. Nieto G, Ros G and Castillo J: Antioxidant and Antimicrobial Properties of Rosemary (*Rosmarinus officinalis*, L.): A Review. Medicines (Basel) 2018; 5(3):

98. doi: 10.3390/medicines5030098. PMID: 30181448; PMCID: PMC6165352.
6. Areti A, Komirishetty P, Kalvala AK, Nellaiappan K and Kumar A: Rosmarinic Acid Mitigates Mitochondrial Dysfunction and Spinal Glial Activation in Oxaliplatin-induced Peripheral Neuropathy. Mol Neurobiol 2018; 55(9): 7463-7475. doi: 10.1007/s12035-018-0920-4. Epub 2018 Feb 9. PMID: 29427084.
7. Todorova V, Ivanov K, Delattre C, Nalbantova V, Karcheva-Bahchevanska D and Ivanova S: Plant Adaptogens-History and Future Perspectives. Nutrients 2021; 13(8): 2861. doi: 10.3390/nu13082861. PMID: 34445021; PMCID: PMC8398443.
8. Wrobel-Biedrawa D and Podolak I: Anti-Neuroinflammatory Effects of Adaptogens: A Mini-Review. Molecules 2024; 29(4): 866. doi: 10.3390/molecules29040866. PMID: 38398618; PMCID: PMC10891670.
9. Panossian A: Understanding adaptogenic activity: specificity of the pharmacological action of adaptogens and other phytochemicals. Ann N Y Acad Sci 2017; 1401(1): 49-64. doi: 10.1111/nyas.13399. Epub 2017 Jun 22. PMID: 28640972
10. Panossian AG, Efferth T, Shikov AN, Pozharitskaya ON, Kuchta K, Mukherjee PK, Banerjee S, Heinrich M, Wu W, Guo DA and Wagner H: Evolution of the adaptogenic concept from traditional use to medical systems: Pharmacology of stress- and aging-related diseases. Med Res Rev 2021; 41(1): 630-703. doi: 10.1002/med.21743. Epub 2020 Oct 25. PMID: 33103257; PMCID: PMC7756641.
11. Lopresti AL, Smith SJ and Drummond PD: Modulation of the hypothalamic-pituitary-adrenal (HPA) axis by plants and phytonutrients: a systematic review of human trials. Nutr Neurosci 2022; 25(8): 1704-1730. doi: 10.1080/1028415X.2021.1892253. Epub 2021 Mar 2. PMID: 33650944.
12. de Oliveira JR, Camargo SEA and de Oliveira LD: *Rosmarinus officinalis* L. (rosemary) as therapeutic and prophylactic agent. J Biomed Sci 2019; 26(1): 5. doi: 10.1186/s12929-019-0499-8. PMID: 30621719; PMCID: PMC6325740.
13. Faridzadeh A, Salimi Y, Ghasemirad H, Kargar M, Rashtchian A, Mahmoudvand G, Karimi MA, Zerangian N, Jahani N, Masoudi A, SadeghianDastjerdi B, Salavatizadeh M, Sadeghsalehi H and Deravi N: Neuroprotective Potential of Aromatic Herbs: Rosemary, Sage, and Lavender. Front. Neurosci 2022; 16: 909833. doi: 10.3389/fnins.2022.909833
14. Hitl M, Kladar N, Gavarić N and Božin B: Rosmarinic Acid-Human Pharmacokinetics and Health Benefits. Planta Med 2021; 87(4): 273-282. doi: 10.1055/a-1301-8648. Epub 2020 Dec 7. PMID: 33285594.
15. Guan H, Luo W, Bao B, Cao Y, Cheng F, Yu S, Fan Q, Zhang L, Wu Q and Shan M: A Comprehensive Review of Rosmarinic Acid: From Phytochemistry to Pharmacology and Its New Insight. Molecules 2022; 27(10): 3292. doi: 10.3390/molecules27103292. PMID: 35630768; PMCID: PMC9143754.
16. Eszter Trocsanyi, Zsuzsanna Gyorgy and Eva Zamborine-Nemeth: New insights into rosmarinic acid biosynthesis based on molecular studies, Current Plant Biology 2020; 23: 100162. doi.org/10.1016/j.cpb.2020.100162.
17. Maike Petersen, Yana Abdullah, Johannes Benner, David Eberle, Katja Gehlen, Stephanie Hücherig, Verena Janiak, Kyung Hee Kim, Marion Sander, Corinna Weitzel and Stefan Wolters: Evolution of rosmarinic acid biosynthesis, Photochemistry 2009; 70; 15–16, Pages 1663-1679, doi.org/10.1016/j.phytochem.2009.05.010.
18. El Kantar S, Yassin A and Nehmeh B: Deciphering the therapeutical potentials of rosmarinic acid. Sci Rep 2022; 12: 15489. https://doi.org/10.1038/s41598-022-19735-y
19. Incollingo Rodriguez AC, Epel ES, White ML, Standen EC, Seckl JR and Tomiyama AJ: Hypothalamic-pituitary-adrenal axis dysregulation and cortisol activity in obesity: A systematic review. Psychoneuroendocrinology 2015; 62: 301-18. doi: 10.1016/j.psyneuen.2015.08.014. Epub 2015 Aug 21. PMID: 26356039.
20. Chockalingam, Nirmala & Muruhan S: Anti-inflammatory properties of rosmarinic acid - A review. International Journal of Research in Pharmaceutical Sciences 2017; 8: 656-662
21. Anil Kumar Kalvala, A. Vijay Kumar, G. Chayanika, S. Bhoomika, K. Rahul and Ashutosh Kumar: Chapter 9 - Rosmarinic acid and mitochondria, Editor(s): Marcos Roberto de Oliveira, Mitochondrial Physiology and Vegetal Molecules, Academic Press 2021; 209-231. https://doi.org/10.1016/B978-0-12-821562-3.00030-7.
22. Dunlavey CJ: Introduction to the Hypothalamic-Pituitary-Adrenal Axis: Healthy and Dysregulated Stress Responses, Developmental Stress and Neurodegeneration. J Undergrad Neurosci Educ 2018; 16(2): 59-60. PMID: 30057514; PMCID: PMC6057754
23. Knezevic E, Nenic K, Milanovic V and Knezevic NN: The role of cortisol in chronic stress, neurodegenerative diseases, and psychological disorders. Cells 2023; 12(23): 2726. doi: 10.3390/cells12232726. PMID: 38067154; PMCID: PMC10706127.
24. al-Sereiti MR, Abu-Amer KM and Sen P: Pharmacology of rosemary (*Rosmarinus officinalis* Linn.) and its therapeutic potentials. Indian J Exp Biol 1999; 37(2): 124-30. PMID: 10641130.
25. Hussain SM, Syeda AF, Alshammari M, Alnasser S, Alenzi ND, Alanazi ST and Nandakumar K: Cognition enhancing effect of rosemary (*Rosmarinus officinalis* L.) in lab animal studies: a systematic review and meta-analysis. Braz J Med Biol Res 2022; 55: 11593. doi: 10.1590/1414-431X2021e11593. PMID: 35170682; PMCID: PMC8851910.
26. Jiuseng Zeng, ZhiqiangXie, Li Chen, Xi Peng, Fei Luan, Jingwen Hu, Hongxiao Xie, Rong Liu and Nan Zeng: Rosmarinic acid alleviate CORT-induced depressive-like behavior by promoting neurogenesis and regulating BDNF/TrkB/PI3K signaling axis. Biomedicine & Pharmacotherapy 2024; 170, doi.org/10.1016/j.biopha.2023.115994.
27. Araki R, Sasaki K, Onda H, Nakamura S, Kassai M, Kaneko T, Isoda H and Hashimoto K: Effects of Continuous Intake of Rosemary Extracts on Mental Health in Working Generation Healthy Japanese Men: Post-Hoc Testing of a Randomized Controlled Trial. Nutrients 2020; 12(11): 3551. doi: 10.3390/nu12113551. PMID: 33233510; PMCID: PMC7699484.
28. Yang M, Yin Y, Wang F, Bao X, Long L, Tan B, Yin Y and Chen J: Effects of dietary rosemary extract supplementation on growth performance, nutrient digestibility, antioxidant capacity, intestinal morphology, and microbiota of weaning pigs. J Anim Sci 2021; 99(9): 237. doi: 10.1093/jas/skab237. PMID: 34370023; PMCID: PMC8420665.
29. Perogamvros I, Ray D & Trainer P: Regulation of cortisol bioavailability effects on hormone measurement and action. Nat Rev Endocrinol 2012; 8: 717–727. https://doi.org/10.1038/nrendo.2012.134

30. Chapman K, Holmes M and Seckl J: 11β-hydroxysteroid dehydrogenases: intracellular gate-keepers of tissue glucocorticoid action. Physiol Rev 2013; 93(3): 1139-206. doi: 10.1152/physrev.00020.2012. PMID: 23899562; PMCID: PMC3962546.
31. Nadeem M, Imran M, Aslam Gondal T, Imran A, Shahbaz, M Muhammad Amir R, Wasim Sajid M, Batool Qaisrani T, Atif M and Hussain G: Therapeutic Potential of Rosmarinic Acid: A Comprehensive Review. Appl Sci 2019; 9: 3139. https://doi.org/10.3390/app9153139
32. Andrade JM, Dos Santos Passos C, Kieling Rubio MA, Mendonça JN, Lopes NP and Henriques AT: Combining *in-vitro* and *in-silico* approaches to evaluate the multifunctional profile of rosmarinic acid from *Blechnum brasiliense* on targets related to neurodegeneration. Chem Biol Interact 2016; 254: 135-45. doi: 10.1016/j.cbi.2016.06.005. Epub 2016 Jun 4. PMID: 27270453.
33. Teleanu RI, Niculescu AG, Roza E, Vladacenco O, Grumezescu AM and Teleanu DM: Neurotransmitters-key factors in neurological and neurodegenerative disorders of the central nervous system. Int J Mol Sci 2022; 23(11): 5954. doi: 10.3390/ijms23115954. PMID: 35682631; PMCID: PMC9180936.
34. Hussain LS, Reddy V and Maani CV: Physiology, Noradrenergic Synapse. 2023 1. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing 2024; PMID: 31082021.
35. Nimgampalle M, Chakravarthy H, Sharma S, Shree S, Bhat AR, Pradeepkiran JA and Devanathan V: Neurotransmitter systems in the etiology of major neurological disorders: Emerging insights and therapeutic implications. Ageing Res Rev 2023; 89: 101994. doi: 10.1016/j.arr.2023.101994. Epub 2023 Jun 28. PMID: 37385351.
36. Naoi M, Maruyama W and Shamoto-Nagai M: Type A monoamine oxidase and serotonin are coordinately involved in depressive disorders: from neurotransmitter imbalance to impaired neurogenesis. J Neural Transm (Vienna) 2018; 125(1): 53-66. doi: 10.1007/s00702-017-1709-8. Epub 2017 Mar 14. PMID: 28293733.
37. Fallarini S, Miglio G, Paoletti T, Minassi A, Amoruso A, Bardelli C, Brunelleschi S, Lombardi G. Clovamide and rosmarinic acid induce neuroprotective effects in *in-vitro* models of neuronal death. Br J Pharmacol 2009; 157(6): 1072-84. doi: 10.1111/j.1476-5381.2009.00213.x. Epub 2009 May 21. PMID: 19466982; PMCID: PMC2737666.
38. Hase T, Shishido S and Yamamoto S: Rosmarinic acid suppresses Alzheimer's disease development by reducing amyloid β aggregation by increasing monoamine secretion. Sci Rep 2019; 9: 8711. https://doi.org/10.1038/s41598-019-45168-1
39. Ahmad Nasiri and Masoomeh Mo'tamed Boroomand: The effect of rosemary essential oil inhalation on sleepiness and alertness of shift-working nurses: A randomized, controlled field trial Complementary Therapies in Clinical Practice 2021; 43. https://doi.org/10.1016/j.ctcp.2021.101326.
40. Gambini J and Stromsnes K: Oxidative Stress and Inflammation: From Mechanisms to Therapeutic Approaches. Biomedicines 2022; 10(4): 753. doi: 10.3390/biomedicines10040753. PMID: 35453503; PMCID: PMC9031318.
41. Janciauskiene S: The beneficial effects of antioxidants in health and diseases. Chronic ObstrPulm Dis 2020; 7(3): 182-202. doi: 10.15326/jcopdf.7.3.2019.0152. PMID: 32558487; PMCID: PMC7857719.
42. Munoz-munoz JL, Garcia-molina F, Ros E, Tudela J, Garcia-canovas F and Rodriguez-lopez JN: Prooxidant and antioxidant activities of rosmarinic acid. Journal of Food Biochemistry 2013; 37: 396-408. https://doi.org/10.1111/j.1745-4514.2011.00639.x
43. Sadeghi A, Bastin AR and Ghahremani H: The effects of rosmarinic acid on oxidative stress parameters and inflammatory cytokines in lipopolysaccharide-induced peripheral blood mononuclear cells. Mol Biol Rep 2020; 47: 3557–3566 (). https://doi.org/10.1007/s11033-020-05447-x
44. Hejun Ren, XiongJin, Chenguang Li, Tingting Li, Yang Liu and Rui Zhou: Rosmarinic acid enhanced Fe(III)-mediated Fenton oxidation removal of organic pollutants at near neutral pH. Science of The Total Environment 2020; 736. https://doi.org/10.1016/j.scitotenv.2020.139528
45. Ting-ting Chai, Yang-na Huang, Shao-tian Ren, Dan-li Jin, Jing-jing Fu, Jun-yanGuo and Yue-wen Chen: Inhibitory effects of ultrasonic and rosmarinic acid on lipid oxidation and lipoxygenase in large yellow croaker during cold storage, Ultrasonics Sonochemistry 2023; 92. https://doi.org/10.1016/j.ultsonch.2022.106229
46. Lee HJ, Cho HS, Park E, Kim S, Lee SY, Kim CS, Kim DK, Kim SJ and Chun HS: Rosmarinic acid protects human dopaminergic neuronal cells against hydrogen peroxide-induced apoptosis. Toxicology 2008; 250(2-3): 109-15. doi: 10.1016/j.tox.2008.06.010. Epub 2008 Jul 4. PMID: 18644421.
47. Nyandwi JB, Ko YS, Jin H, Yun SP, Park SW and Kim HJ: Rosmarinic acid increases macrophage cholesterol efflux through regulation of abca1 and abcg1 in different mechanisms. Int J Mol Sci 2021; 22(16): 8791. doi: 10.3390/ijms22168791. PMID: 34445501; PMCID: PMC8395905.
48. Noor S, Mohammad T and Rub MA: Biomedical features and therapeutic potential of rosmarinic acid. Arch. Pharm. Res 2022; 45: 205–228. https://doi.org/10.1007/s12272-022-01378-2
49. Araki R, Sasaki K, Onda H, Nakamura S, Kassai M, Kaneko T, Isoda H and Hashimoto K: Effects of continuous intake of rosemary extracts on mental health in working generation healthy japanese men: post-hoc testing of a randomized controlled trial. Nutrients 2020; 12(11): 3551. doi: 10.3390/nu12113551. PMID: 33233510; PMCID: PMC7699484.
50. Beilei Lu, Cuixian Li, Luxia Jing, Fan Zhuang, Huijing Xiang, Yu Chen and Beijian Huang: Rosmarinic acid nanomedicine for rheumatoid arthritis therapy: Targeted RONS scavenging and macrophage repolarization. Journal of Controlled Release 2023; 362: 631-646. doi.org/10.1016/j.jconrel.2023.09.012
51. Caroline Leal Rodrigues Soares, PolratWilairatana, Larissa Rodrigues Silva, Polyanna Silva Moreira, Nayana Maria Medeiros Vilar Barbosa, Pablo Rayff da Silva, Henrique Douglas MeloCoutinho, Irwin Rose Alencar de Menezes and Cícero Francisco Bezerra Felipe: Biochemical aspects of the inflammatory process: A narrative review. Biomedicine & Pharmacotherapy 2023; 168: doi.org/10.1016/j.biopha.2023.11576
52. Cai G, Lin F, Wu D, Lin C, Chen H, Wei Y, Weng H, Chen Z, Wu M, Huang E, Ye Z and Ye Q: Rosmarinic acid inhibits mitochondrial damage by alleviating unfolded protein response. Front Pharmacol 2022; 13: 859978. doi: 10.3389/fphar.2022.859978. PMID: 35652041; PMCID: PMC9149082
53. Vakifahmetoglu-Norberg H, Ouchida AT and Norberg E: The role of mitochondria in metabolism and cell death.

Biochem Biophys Res Commun 2017; 482(3): 426-431. doi: 10.1016/j.bbrc.2016.11.088. Epub 2017 Feb 3. PMID: 28212726.

54. Pere Puigserver and Bruce M: Spiegelman, peroxisome proliferator-activated receptor-γ coactivator 1α (pgc-1α): transcriptional coactivator and metabolic regulator. Endocrine Reviews 2003; 24(1): 78–90, https://doi.org/10.1210/er.2002-0012
55. Maliheh Entezari, Danial Hashemi, Afshin Taheriazam, Amirhossein Zabolian, Shima Mohammadi, Farima Fakhri, Mehrdad Hashemi, Kiavash Hushmandi, Milad Ashrafizadeh, Ali Zarrabi, Yavuz Nuri Ertas, Sepideh Mirzaei and Saeed Samarghandian: AMPK signaling in diabetes mellitus, insulin resistance and diabetic complications: A pre-clinical and clinical investigation. Biomedicine & Pharmacotherapy 2022; 146. doi.org/10.1016/j.biopha.2021.112563.
56. Jayanthy G, Roshana Devi V, Ilango K and Subramanian SP: Rosmarinic acid mediates mitochondrial biogenesis in Insulin resistant skeletal muscle through activation of AMPK. J Cell Biochem 2017; 118(7): 1839-1848. doi: 10.1002/jcb.25869. Epub 2017 Mar 21. PMID: 28059465
57. Achour M, Ben Salem I, Ferdousi F, Nouira M, Ben Fredj M, Mtiraoui A, Isoda H and Saguem S: Rosemary tea consumption alters peripheral anxiety and depression biomarkers: a pilot study in limited healthy volunteers. J Am Nutr Assoc 2022; 41(3): 240-249. doi: 10.1080/07315724.2021.1873871. Epub 2021 Feb 10. PMID: 33565922.
58. Manikyam, Hemanth Kumar, Joshi, Sunil, Tripathi, Prathibha, Joshi, Jyoti, Balasubramanian, Jayaram, Udhyog, Jadibuti and Assistant: Arabian Journal of Medicinal & Aromatic Plants Extraction, Purification and quantification of Ursolic acid Ursolic extraction process from Rosemary officinalis leaves of Nepal Cultivar 2023; 9. 54-64. DOI: https://doi.org/10.48347/IMIST.PRSM/ajmap-v9i2.29213

How to cite this article:
Manikyam HK, Aeri V, Dhanaseelan J and Mani J: Unlocking the adaptogenic power of rosemary (*Rosmarinus officinalis*): a comprehensive exploration of its pharmacological potential for stress resilience and holistic well-being. Int J Pharm Sci & Res 2025; 16(1): 47-57. doi: 10.13040/IJPSR.0975-8232.16(1).47-57.