Review Article

Int Jou Hea Bio Sci, 4(2), 2023, 69-72

International Journal of
Health care and Biological Sciences

Content available at www.saap.org.in Online ISSN: 2582-7499

Open Access

IMMUNOMODULATORY POTENTIAL OF APIUM GRAVEOLENS: EMERGING PHARMACOLOGICAL PERSPECTIVES

Archita Tiwari*[1], Bharat Mishra[2]

[1]Faculty of Pharmacy, Khwaja Moinuddin Chishti Language University, Lucknow

[2]Institute of Pharmacy, Dr. Shakuntala Misra National Rehabilitation University, Lucknow

Article History

Received on: 14-02-2023

Revised on: 22-03-2023

Accepted on: 03-05-2023

Abstract

Apium graveolens has become a promising phytotherapeutic agent with multiple pharmacological applications; but its immunomodulatory effects have not been well studied in a mechanistic approach. This is a thorough and integrative review of the immunomodulatory properties of Apium graveolens, focusing on its bioactive compounds, molecular targets, and translational significance. Apigenin, luteolin, and phthalides are the important phytochemicals that have pleiotropic actions because they regulate the key immune pathways, nuclear factor-kappa B (NF-KB) signaling, cytokine interactions, and oxidative stress-mediated immune responses. All of these compounds affect the innate and adaptive immunity by modulating the macrophage activation, T-cell responses, and the inflammatory mediators. Notably, this review suggests a single mechanistic model whereby Apium graveolens acts as a multitarget immunomodulator by integrating the NF- kBcytokine axis with the oxidative stress-immune interface. Although there is strong preclinical evidence, there are still important gaps in clinical confirmation, dose standardisation and immune specific studies. This paper demonstrates the promise of Apium graveolens as a new candidate to develop into immunotherapeutics and emphasizes the necessity of sophisticated experimental and clinical research to transform its pharmacological potential into clinical use.

Keywords: *Apium graveolens, Immunomodulation, NF-kB.*

***Corresponding Author**

Archita Tiwari

Introduction

The immune system has also been developed to safeguard the host against a universe of pathogenic microbes who in turn are continually evolving [1]. The immune system, also assists the host in getting rid of toxic or allergic substances, which are introduced into the body via mucosal surfaces. At the center of the processes of mobilizing an immune response to an invading pathogen, toxin or allergen is the capacity of the immune system to differentiate self and nonself. Both innate and adaptive systems allow the host to detect and get rid of pathogenic microbes and both of them involve self-nonself discrimination [2]. Plant-derived immunomodulators have received growing interest over recent years because they are safe, readily available, and have a complex mode of action [3, 4]. Natural products have been demonstrated to affect immune response, through regulation of cytokine production, oxidative stress pathways, and cellular signaling pathways [5].

Celery is a commercially significant seed spice that is a member of the family Umbelliferrae. Celery is consumed in different forms which include fresh herb, stalk, seeds, oil and oleoresin as food flavors as well as medicinal products [6]. The celery seed has 2% volatile oil that is used in the perfumery industry as well as in flavoring of foods. Approximately 60% and 20% of the oil consists of limonene and selinene, respectively [7]. Nonetheless, 3-n-butyl-4-5-dihydrophthalide (sedanenolide), 3-n-butyl phthalide, sedanolide, and sedanonic anhydride are the key aroma compounds of the oil that are in very low concentrations (1 3%). Celery has 15 percent fatty oil which includes the fatty acids: petroselenic (64.3%), oleic (8.1), linoleic (18.0) and palmitic acids (0.6). Phthalides, particularly sedanenaloide have numerous health advantages [8].

This review is the first to offer an integrated immunological framework of Apium graveolens: it presents the multitarget immunomodulatory mechanisms of this plant in contrast to prior reviews, which have concentrated on antioxidant and anti-inflammatory effects.

Chemical constituents: The major phytochemical assay on the seed extract of Apium graveolens reveals that carbohydrates, flavonoids, alkaloids, steroids and glycosides are present in the methanolic extract [9]. The plant contained furocoumarins and phenols. Celerin, bergapten, apiumoside, apiumetin, apigravrin, osthenol, isopimpinellin, isoimperatorin, celereoside, 5 and 8-hydroxy methoxypsoralen were found in furocoumarins. Phenols (155.41-177.23mg/100g) included graveobioside A and B, apiin, apigenin, isoquercitrin, tannins (3.89-4.39 mg /100g) and phytic acid (19.85-22.05mg/g) [10, 11].

Apigenin is a naturally occurring flavonoid that is very abundant in Apium graveolens and is a key immunomodulator because of its multimodal action on important cellular and molecular pathways [12]. It has been extensively documented to suppress activation of nuclear factor-kappa B (NF-κB) signaling pathway, which inhibits the transcription of pro-inflammatory cytokines tumor necrosis factor-alpha (TNF- 7), interleukin-6 (IL-6) and interleukin-1 (IL-1β) [13].

Besides the regulation of cytokines, apigenin also regulates immune cell functions by affecting the macrophage activation and T-cells responses, and this plays a role in maintaining immune homeostasis [14].

Pharmacological potential:Celery extracts are known to have numerous nutraceutical properties, viz., antioxidant, hypolipidemic, hypoglycemic and anti-platelet aggregation [15].These pharmacological actions are highly ascribed to its bioactive components namely flavonoids like apigenin and luteolin, phenolic acids, volatile oils which are known to be able to exert biological action by various molecular targets. Interestingly, most of these compounds also play a role in controlling immune reactions. As an example, flavonoids were reported to inhibit pro-inflammatory cytokines, prevent the activity of major transcription factors like NF- KB, and regulate the activity of immune cells [16]. Although these encouraging results have been reported, the immunomodulatory power of Apium graveolens has not been actively pursued and most of the existing researches concentrate more on the anti-inflammatory or antioxidant properties than direct immune regulation [17].

Considering the strong interconnectedness between oxidative stress, inflammation and immune activity, it is reasonable to assume that Apium graveolens can have substantial immunomodulatory effects via concerted molecular mechanisms. Hence, a thorough analysis of its contribution to immune modulation is justified. The current review will fill this gap by critically examining the existing evidence on phytochemistry; mechanisms, and therapeutic relevance of Apium graveolens in relation to immunomodulation. The review offers a mechanistic and translational viewpoint in order to bring to the fore the promise of celery as a new candidate in terms of immune-based therapeutic approaches.

Molecular Processes of Apium graveolens.

These immunomodulatory effects of Apium graveolens are facilitated by a complex interaction of molecular signaling pathways that ensure immune homeostasis. One of the main mechanisms is NF-kappaBsignaling, as bioactive compounds such as apigenin and luteolin inhibit the NF-kappaB activation [18]. Celery extracts are effective in the down-regulation of pro-inflammatory genes 12 by inhibiting the process of NF-kB translocation into the nucleus. This results in the direct effect of Cytokine regulation whereby there is a high decrease in production of pro-inflammatory cytokines like TNF-alpha, IL-1beta and IL-6 and at the same time an increase in the production of anti-inflammatory mediators [19, 20]. Moreover, the herb balances the Oxidative stress-immune axis by countering the reactive oxygen species (ROS) and activating the endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase. This decrease in oxidative stress inhibits the second activation of immune cells that is normally a feature of a pro-oxidant environment15. Lastly, A. graveolens affects Apoptosis and immune balance through the regulation of Bcl-2/Bax ratio. Under inflammatory conditions, it may cause apoptosis of overactive immune cells or damaged tissues, thus preventing chronic inflammation and selective survival of functional immune cells [21].

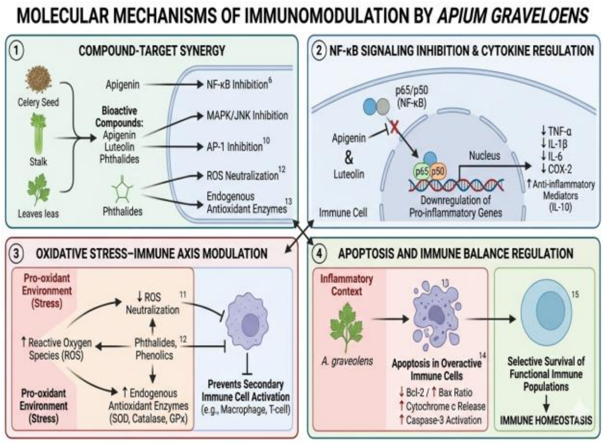

Fig.1 Mechanistic pathways of Apium graveolens for immunomodulation

The medicinal activity of Apium graveolens is based on a particular compound-target interaction guiding its immunomodulatory actions. The main bioactive constituents like apigenin have a strong anti-inflammatory effect by suppressing the NF-kappaBsignaling pathway, which in turn suppresses the release of pro-inflammatory cytokine like TNF-alpha [22]. Incorporated with this, the production of IL-6 through the suppression of the MAPK/JNK phosphorylation and the activation of AP-1 [23, 24], has been demonstrated to be reduced by luteolin a flavone found in abundance in celery. Moreover, celery has special phthalides and phenolic extracts, which have played a vital antioxidant role in neutralizing reactive oxygen species (ROS) and inducing endogenous antioxidant enzymes, thereby reducing the oxidative stress, which often triggers immune dysregulation [25]. This combined molecular strategy enables A. graveolens to stabilize the immune microenvironment as a multi-target agent.

Conclusion

In conclusion, Apium graveolens represents a compelling example of a multitarget phytotherapeutic agent with significant immunomodulatory potential. The results generalized in this review indicate that its biological action cannot be associated to any single compound, but is a resultant effect of a synergistic interaction between flavonoids, especially apigenin and luteolin, and phthalide derivatives, including 3-n-butylphthalide. The combination of these bioactive constituents together regulates important immunological responses, such as the NF-KB pathway, cytokine generation, and the oxidative stress response, restoring immune homeostasis. Notably, this combined action sets APIum graveolens apart as compared to traditional single-target agents and explains its potential to treat complex immune-mediated diseases. However, the existing evidence is still largely preclinical, and lack of specific immunological investigations restricts its translational use. The future research should thus aim at confirming these mechanisms of action in clinically relevant models to prove Apium graveolens as a scientifically supported immunomodulatory agent.

Future Perspectives

Future studies on Apium graveolens ought to focus on the translation of experimental findings to clinical relevance through filling critical gaps in immunopharmacological studies. Rigorous in vivo and clinical studies are essential to validate its efficacy, safety, and therapeutic potential in immune-related disorders. To ensure dose optimization and reproducibility, standardization of plant extracts (quantification of active components, i.e. apigenin, luteolin and phthalides) is essential. More sophisticated omics-based methods, such as transcriptomics, proteomics and metabolomics, are required to clarify specific molecular targets and processes, especially regarding T-cell differentiation, macrophage polarization, and immune memory development. Moreover, bioavailability could be improved through the creation of new delivery systems that could be used to target immunomodulation, including nano formulations. Safe clinical integration will require exploration of herb-drug interactions, and long-term toxicity profiles. Also, newly discovered mechanisms like the gut-immune axis and modulation of the microbiome are promising future research possibilities. Together, the methods will enable the creation of Apium graveolens-based immunotherapeutics and its implementation into evidence-based and personalized medicine.

Acknowledgement

Not Declared

Conflict of Interest

The authors have declared no Conflict of Interest.

Ethical Statement and Inform Consent

Not applicable

Author Contribution

Both are contributed equally.

Funding

Nil

References

1. Sattler, S. J. T. i. o. c. h.; pathology, The role of the immune system beyond the fight against infection. 2017, 3-14.
2. Chaplin, D. D. J. J. o. a.; immunology, c., Overview of the immune response. 2010,*125* (2), S3-S23.
3. Jantan, I.; Ahmad, W.; Bukhari, S. N. A. J. F. i. p. s., Plant-derived immunomodulators: an insight on their preclinical evaluation and clinical trials. 2015,*6*, 655.
4. Zebeaman, M.; Tadesse, M. G.; Bachheti, R. K.; Bachheti, A.; Gebeyhu, R.; Chaubey, K. K. J. B. r. i., Plants and plant-derived molecules as natural immunomodulators. 2023,*2023* (1), 7711297.
5. Medzhitov, R. J. N., Origin and physiological roles of inflammation. 2008,*454* (7203), 428-435.
6. Hussain, M.; Sabri, R.; Zia-Ul-Haq, M.; Riaz, M. J. E. o. M.; Crops, A., Celery. 2023, 1165-1190.
7. Dąbrowska, J. A.; Kunicka-Styczyńska, A.; Śmigielski, K. B. J. J. o. E. O. R., Biological, chemical, and aroma profiles of essential oil from waste celery seeds (Apium graveolens L.). 2020,*32* (4), 308-315.
8. Zhang, Y.; Wang, T.; Wang, X.; Dong, R.; Wang, D.; Zhao, G. J. F. R. I., Apium Graveolens Linn.(celery) seeds: A comprehensive review of phytochemistry profile, pharmacological effects and future trends. 2025, 1-28.
9. Mencherini, T.; Cau, A.; Bianco, G.; Loggia, R. D.; Aquino, R. P.; Autore, G. J. J. o. p.; pharmacology, An extract of Apium graveolens var. dulce leaves: structure of the major constituent, apiin, and its anti-inflammatory properties. 2007,*59* (6), 891-897.
10. Khalil, A.; Nawaz, H.; Ghania, J. B.; Rehman, R.; Nadeem, F. J. I. J. o. C.; Sciences, B., Value added products, chemical constituents and medicinal uses of celery (Apium graveolens L.)–A review. 2015,*8* (2015), 40-8.
11. Li, Z.; Zhou, J.; Ji, L.; Liang, Y.; Xie, S. J. F. R. I., Recent advances in the pharmacological actions of apigenin, its complexes, and its derivatives. 2023,*39* (9), 6568-6601.

12. Shukla, S.; Gupta, S. J. P. r., Apigenin: a promising molecule for cancer prevention. 2010,*27* (6), 962-978.
13. Salehi, B.; Venditti, A.; Sharifi-Rad, M.; Kręgiel, D.; Sharifi-Rad, J.; Durazzo, A.; Lucarini, M.; Santini, A.; Souto, E. B.; Novellino, E. J. I. j. o. m. s., The therapeutic potential of apigenin. 2019,*20* (6), 1305.
14. Hang, N. T.; Uyen, T. T. T.; Van Phuong, N. J. J. o. P.; Analysis, B., Green extraction of apigenin and luteolin from celery seed using deep eutectic solvent. 2022,*207*, 114406.
15. Sowbhagya, H. B., Chemistry, Technology, and Nutraceutical Functions of Celery (Apium graveolens L.): An Overview. *Critical Reviews in Food Science and Nutrition* 2014,*54* (3), 389-398.
16. 16. Kim, H. P.; Son, K. H.; Chang, H. W.; Kang, S. S. J. J. o. p. s., Anti-inflammatory plant flavonoids and cellular action mechanisms. 2004,*96* (3), 229-245.
17. Kawai, T.; Akira, S. J. T. i. m. m., Signaling to NF-κB by Toll-like receptors. 2007,*13* (11), 460-469.
18. Hsieh, L.-C.; Hsieh, S.-L.; Ping, T.-N.; Huang, Y.-C.; Lin, S.-J.; Chi, H.-Y.; Wu, C.-C. J. P. B., Apium graveolens L. alleviates acute lung injury in human A-549 cells by reducing NF-κB and NLRP3 inflammasome signaling. 2025,*63* (1), 1-13.
19. Al-Asmari, A. K.; Athar, M. T.; Kadasah, S. G. J. P. r., An updated phytopharmacological review on medicinal plant of Arab region: Apium graveolens linn. 2017,*11* (21), 13.
20. Jang, S., *Beneficial effect of the flavonoid luteolin on neuroinflammation*. University of Illinois at Urbana-Champaign: 2009.
21. Thuwaini, M. M. J. G. B. P. S., Natural sources as promising future anticancer therapies-A review. 2022,*19*, 084-113.
22. Fathalla, A. S.; Mumtaz, F.; Ramadan, S. S.; Ibrahim, M. A.; El-Khadragy, M. F.; Moneim, A. E. A.; Soliman, D.; Mohamed, S. R. J. F.; Immunology, A., Celery leaf extract attenuates inflammation in a murine model of carrageenan-induced paw edema via modulation of NF-κB and antioxidant pathways. 2026,*37* (1), 2620874.
23. Jang, S.; Kelley, K. W.; Johnson, R. W. J. P. o. t. N. A. o. S., Luteolin reduces IL-6 production in microglia by inhibiting JNK phosphorylation and activation of AP-1. 2008,*105* (21), 7534-7539.
24. Liu, Y.; Jiao, A. J. F. i. I., Flavonoids as Immunoregulators: Molecular Mechanisms in Regulating Immune Cells and Their Therapeutic Applications in Inflammatory Diseases. 2025,*16*, 1703672.
25. Al Disi, S. S.; Anwar, M. A.; Eid, A. H. J. F. i. p., Anti-hypertensive herbs and their mechanisms of action: part I. 2016,*6*, 323.