International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Integrating Bioinformatics to Uncover Anti-inflammatory Mechanisms of Phytochemicals

*Dr. Vinay Kumar Singh**

Information Officer, Centre for Bioinformatics, School of Biotechnology, Institute of Science, Banaras Hindu University, Varanasi, Uttar Pradesh 221005

*E-mail: vinaysingh@bhu.ac.in

ABSTRACT:

Inflammation is a biological response to harmful stimuli, playing a critical role in various diseases, such as cancer, cardiovascular disease, and autoimmune disorders. Phytochemicals, naturally occurring compounds found in plants, have been widely recognized for their anti-inflammatory properties. Bioinformatics offers powerful tools for the systematic analysis of these compounds, enabling the identification of their molecular targets, pathways, and mechanisms of action. This review explores how bioinformatics can be employed to investigate the anti-inflammatory mechanisms of phytochemicals and highlights key bioinformatics approaches, databases, and computational tools that advance phytochemical research. We provide examples of specific phytochemicals that have shown promise in reducing inflammation, each with relevant references.

Keywords: Inflammation, Phytochemicals, Bioinformatics, Anti-inflammatory compounds

1. Introduction:

Inflammation is a crucial physiological process that serves as the body's response to infection, injury, or toxic stimuli. Chronic inflammation, however, is associated with various diseases, including rheumatoid arthritis, cancer, neurodegenerative diseases, and cardiovascular disorders. Phytochemicals, bioactive compounds derived from plants, have demonstrated significant anti-inflammatory potential by modulating signaling pathways and reducing the expression of pro-inflammatory mediators.

With the advancement of bioinformatics, researchers now have robust tools to explore the molecular interactions, gene expression impacts, and therapeutic applications of these phytochemicals. This manuscript focuses on using bioinformatics to uncover the anti-inflammatory mechanisms of phytochemicals and discusses the available computational tools and databases that facilitate such research.

2. Phytochemicals and Inflammation:

Phytochemicals such as flavonoids, alkaloids, terpenoids, and polyphenols exhibit anti-inflammatory properties by interacting with various cellular pathways. For example, flavonoids like quercetin and curcumin inhibit the nuclear factor-kappa B (NF-κB) pathway, a key regulator of inflammation. Similarly, resveratrol modulates tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) signaling, reducing inflammatory cytokine production.

3. Bioinformatics Approaches in Phytochemical Research:

3.1. Molecular Docking and Virtual Screening:

Molecular docking is a computational technique that predicts the interaction between a phytochemical and its target protein. This helps identify binding sites and assess the efficacy of phytochemicals in inhibiting pro-inflammatory proteins. Quercetin, for example, has been shown to bind effectively to cyclooxygenase-2 (COX-2), a key enzyme involved in inflammation.

Virtual screening is another bioinformatics approach that tests large libraries of compounds *in silico* to identify potential inhibitors of inflammation-related proteins. It enables the identification of novel phytochemicals from natural product databases like ZINC and ChEMBL.

3.2. Gene Expression Profiling and Network Analysis:

Gene expression profiling using databases like GEO and ArrayExpress allows researchers to examine gene expression changes after treatment with specific phytochemicals. For instance, curcumin has been shown to downregulate genes involved in the NF-κB pathway.

Network analysis, using tools such as STRING and Cytoscape, helps identify how phytochemicals modulate complex signaling pathways. Protein-protein interaction (PPI) networks reveal how phytochemicals influence molecular interactions in inflammation.

3.3. Systems Biology and Omics Integration:

The integration of omics data, such as genomics, transcriptomics, proteomics, and metabolomics, provides a holistic view of the effects of phytochemicals on inflammation. Bioinformatics platforms like Ingenuity Pathway Analysis (IPA) and KEGG facilitate mapping the systemic effects of phytochemicals on inflammation-related pathways. Metabolomics studies, for example, have shown that resveratrol modulates lipid metabolism and oxidative stress pathways.

4. Databases for Phytochemical Research:

Several databases aid bioinformatics research on phytochemicals, including:

TCMSP (Traditional Chinese Medicine Systems Pharmacology Database): Offers data on phytochemicals' pharmacokinetics and molecular targets.

NPASS (Natural Products Activity and Species Source Database): Provides information on natural products, including their anti-inflammatory activity.

PubChem: A comprehensive chemical database for retrieving information on the biological activities of phytochemicals.

5. Phytochemicals with Anti-inflammatory Properties:

The screening identified potent anti-inflammatory compounds (see Table 1), demonstrating broad applications in anti-inflammatory therapies by modulating pathways like NF-κB, COX-2, and pro-inflammatory cytokines.

Table: Potent Anti-inflammatory Compounds

Compound	**Plant Source**	**Plant Part**
Curcumin	Turmeric (*Curcuma longa*)	Rhizome
Quercetin	Onion (*Allium cepa*)	Bulb
Resveratrol	Grapes (*Vitis vinifera*)	Skin
Epigallocatechin gallate (EGCG)	Green tea (*Camellia sinensis*)	Leaves
Berberine	Goldenseal (*Hydrastis canadensis*)	Root
Apigenin	Chamomile (*Matricaria chamomilla*)	Flowers
Boswellic acids	Frankincense (*Boswellia serrata*)	Resin
Gingerol	Ginger (*Zingiberofficinale*)	Rhizome
Hesperidin	Orange (*Citrus sinensis*)	Peel
Kaempferol	Broccoli (*Brassica oleracea*)	Flowers, Leaves
Luteolin	Celery (*Apiumgraveolens*)	Stems, Leaves
Oleuropein	Olive (*Olea europaea*)	Leaves, Fruit
Capsaicin	Chili pepper (*Capsicum spp.*)	Fruit
Thymoquinone	Black cumin (*Nigella sativa*)	Seeds
Silymarin	Milk thistle (*Silybummarianum*)	Seeds
Genistein	Soybean (*Glycine max*)	Seeds
Catechin	Cocoa (*Theobroma cacao*)	Seeds

Baicalin	Baikal skullcap (*Scutellariabaicalensis*)	Root
Fisetin	Strawberry (*Fragaria × ananassa*)	Fruit
Pterostilbene	Blueberry (*Vaccinium spp.*)	Fruit
Allicin	Garlic (*Allium sativum*)	Bulb
Gallic acid	Pomegranate (*Punicagranatum*)	Fruit
Naringenin	Grapefruit (*Citrus paradisi*)	Fruit, Peel
Myricetin	Red wine (*Vitis vinifera*)	Skin, Fruit
Apigenin	Parsley (*Petroselinum crispum*)	Leaves, Stems
Carnosic acid	Rosemary (*Rosmarinus officinalis*)	Leaves
Rosmarinic acid	Basil (*Ocimumbasilicum*)	Leaves
Ellagic acid	Blackberry (*Rubusfruticosus*)	Fruit
Emodin	Rhubarb (*Rheum spp.*)	Root, Stems
Ursolic acid	Apples (*Malus domestica*)	Peel
Diosmin	Lemon (*Citrus limon*)	Peel
Shogaol	Ginger (*Zingiberofficinale*)	Rhizome
Escin	Horse chestnut (*Aesculus hippocastanum*)	Seeds
Astaxanthin	Microalgae (*Haematococcuspluvialis*)	Whole Algae
Rutin	Buckwheat (*Fagopyrum esculentum*)	Leaves, Seeds
Isorhamnetin	Sea buckthorn (*Hippophaerhamnoides*)	Fruit, Leaves
Arctigenin	Burdock (*Arctiumlappa*)	Root
Ginsenosides	Ginseng (*Panax ginseng*)	Root
Magnolol	Magnolia (*Magnolia officinalis*)	Bark
Chlorogenic acid	Coffee (*Coffea spp.*)	Seeds
Rhein	Rhubarb (*Rheum spp.*)	Root, Stems
Xanthohumol	Hops (*Humulus lupulus*)	Flowers
Honokiol	Magnolia (*Magnolia officinalis*)	Bark
Baicalein	Baikal skullcap (*Scutellariabaicalensis*)	Root
Piperine	Black pepper (*Piper nigrum*)	Fruit
Lycopene	Tomato (*Solanum lycopersicum*)	Fruit
Caffeic acid	Coffee (*Coffea spp.*)	Seeds
Phyllanthin	Phyllanthus (*Phyllanthus niruri*)	Whole Plant
Tanshinone	Red sage (*Salvia miltiorrhiza*)	Root
Quassin	Quassia (*Quassiaamara*)	Bark, Wood
Andrographolide	Andrographis (*Andrographis paniculata*)	Leaves, Stem
Ajoene	Garlic (*Allium sativum*)	Bulb
Apocynin	Canadian hemp (*Apocynumcannabinum*)	Root
Sesamin	Sesame (*Sesamum indicum*)	Seeds

Curculigoside	Golden eye grass (*Curculigoorchioides*)	Rhizome
Tetrandrine	Stephania (*Stephania tetrandra*)	Root
Astragalin	Astragalus (*Astragalus membranaceus*)	Root
Isorhapontigenin	Rhubarb (*Rheum spp.*)	Root, Stems
Picroside	Kutki (*Picrorhizakurroa*)	Rhizome
Withaferin A	Ashwagandha (*Withaniasomnifera*)	Root, Leaves
Betulinic acid	Birch (*Betula spp.*)	Bark
Oleanolic acid	Olive (*Olea europaea*)	Leaves, Fruit
Plumbagin	Leadwort (*Plumbago zeylanica*)	Root, Leaves
Madecassoside	Gotu kola (*Centellaasiatica*)	Leaves, Stems
Salvianolic acid	Red sage (*Salvia miltiorrhiza*)	Root
Arbutin	Bearberry (*Arctostaphylos uva-ursi*)	Leaves
Galangin	Galangal (*Alpiniaofficinarum*)	Rhizome
Gallocatechin	Green tea (*Camellia sinensis*)	Leaves
Mangiferin	Mango (*Mangiferaindica*)	Leaves, Fruit
Humulone	Hops (*Humulus lupulus*)	Flowers
Amentoflavone	Ginkgo (*Ginkgo biloba*)	Leaves
Asiaticoside	Gotu kola (*Centellaasiatica*)	Leaves, Stems
Echinacoside	Echinacea (*Echinacea purpurea*)	Root, Leaves
Bacoside	Brahmi (*Bacopa monnieri*)	Leaves
Cinnamaldehyde	Cinnamon (*Cinnamomumverum*)	Bark
Punicalagin	Pomegranate (*Punicagranatum*)	Fruit, Peel
Lapachol	Pau d'arco (*Tabebuia avellanedae*)	Bark
Diallyl sulfide	Garlic (*Allium sativum*)	Bulb
Hispidulin	Safflower (*Carthamustinctorius*)	Flowers
Salvigenin	Sage (*Salvia officinalis*)	Leaves
Formononetin	Red clover (*Trifoliumpratense*)	Leaves, Flowers
Licochalcone A	Licorice (*Glycyrrhiza glabra*)	Root
Auraptene	Citrus (*Citrus aurantium*)	Peel
Pinocembrin	Honey (*Apis mellifera*)	Honey
Bavachinin	Psoralea (*Psoraleacorylifolia*)	Seeds
Isoliquiritigenin	Licorice (*Glycyrrhiza glabra*)	Root
Tectochrysin	Honey (*Apis mellifera*)	Honey
Pristimerin	Celastrus (*Celastruspaniculatus*)	Seeds, Leaves
Piperlongumine	Long pepper (*Piper longum*)	Fruit
Curzerenone	Javanese ginger (*Curcuma zedoaria*)	Rhizome
Erythrodiol	Olive (*Olea europaea*)	Leaves, Fruit

Cardamonin	Cardamom (*Elettariacardamomum*)	Seeds
Beta-caryophyllene	Clove (*Syzygiumaromaticum*)	Buds

6. Conclusion:

The integration of bioinformatics into phytochemical research has significantly advanced our understanding of their anti-inflammatory mechanisms. Molecular docking, gene expression profiling, and omics integration have provided invaluable insights into the molecular targets and pathways modulated by phytochemicals. Future research should focus on improving omics integration and developing advanced bioinformatics tools to predict phytochemicals' clinical potential more effectively. By leveraging bioinformatics, we can harness these natural compounds' therapeutic potential to treat chronic inflammatory diseases.

References Used

Aggarwal, B. B., Sundaram, C., Malani, N., & Ichikawa, H. (2007). Curcumin: the Indian solid gold. Advances in experimental medicine and biology, 595, 1–75. https://doi.org/10.1007/978-0-387-46401-5_1

Alakurtti, S., Mäkelä, T., Koskimies, S., & Yli-Kauhaluoma, J. (2006). Pharmacological properties of the ubiquitous natural product betulin. European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences, 29(1), 1–13. https://doi.org/10.1016/j.ejps.2006.04.006

Jesus, J. A., Lago, J. H., Laurenti, M. D., Yamamoto, E. S., & Passero, L. F. (2015). Antimicrobial activity of oleanolic and ursolic acids: an update. Evidence-based complementary and alternative medicine : eCAM, 2015, 620472. https://doi.org/10.1155/2015/620472

Ammon H. P. (2006). Boswellic acids in chronic inflammatory diseases. Planta medica, 72(12), 1100–1116. https://doi.org/10.1055/s-2006-947227

Ammon H. P. (2016). Boswellic Acids and Their Role in Chronic Inflammatory Diseases. Advances in experimental medicine and biology, 928, 291–327. https://doi.org/10.1007/978-3-319-41334-1_13

Arts, I. C., van de Putte, B., & Hollman, P. C. (2000). Catechin contents of foods commonly consumed in The Netherlands. 1. Fruits, vegetables, staple foods, and processed foods. Journal of agricultural and food chemistry, 48(5), 1746–1751. https://doi.org/10.1021/jf000025h

Attele, A. S., Wu, J. A., & Yuan, C. S. (1999). Ginseng pharmacology: multiple constituents and multiple actions. Biochemical pharmacology, 58(11), 1685–1693. https://doi.org/10.1016/s0006-2952(99)00212-9

Kim, Y., Lee, H., Park, H. J., Kim, M. K., Kim, Y. I., Kim, H. J., Bae, S. K., Kim, Y. J., & Bae, M. K. (2023). Hispidulin Inhibits the Vascular Inflammation Triggered by Porphyromonas gingivalis Lipopolysaccharide. Molecules (Basel, Switzerland), 28(18), 6717. https://doi.org/10.3390/molecules28186717

Baur, J. A., & Sinclair, D. A. (2006). Therapeutic potential of resveratrol: the in vivo evidence. Nature reviews. Drug discovery, 5(6), 493–506. https://doi.org/10.1038/nrd2060

Benavente-García, O., & Castillo, J. (2008). Update on uses and properties of citrus flavonoids: new findings in anticancer, cardiovascular, and anti-inflammatory activity. Journal of agricultural and food chemistry, 56(15), 6185–6205. https://doi.org/10.1021/jf8006568

Kung, F. P., Lim, Y. P., Chao, W. Y., Zhang, Y. S., Yu, H. I., Tai, T. S., Lu, C. H., Chen, S. H., Li, Y. Z., Zhao, P. W., Yen, Y. P., & Lee, Y. R. (2021). Piperlongumine, a Potent Anticancer Phytotherapeutic, Induces Cell Cycle Arrest and Apoptosis In Vitro and In Vivo through the ROS/Akt Pathway in Human Thyroid Cancer Cells. Cancers, 13(17), 4266. https://doi.org/10.3390/cancers13174266

Binns, S. E., Livesey, J. F., Arnason, J. T., & Baum, B. R. (2002). Phytochemical variation in echinacea from roots and flowerheads of wild and cultivated populations. Journal of agricultural and food chemistry, 50(13), 3673–3687. https://doi.org/10.1021/jf011439t

Boots, A. W., Haenen, G. R., & Bast, A. (2008). Health effects of quercetin: from antioxidant to nutraceutical. European journal of pharmacology, 585(2-3), 325–337. https://doi.org/10.1016/j.ejphar.2008.03.008

Borek C. (2001). Antioxidant health effects of aged garlic extract. The Journal of nutrition, 131(3s), 1010S–5S. https://doi.org/10.1093/jn/131.3.1010S

Forester, S. C., & Lambert, J. D. (2011). The role of antioxidant versus pro-oxidant effects of green tea polyphenols in cancer prevention. Molecular nutrition & food research, 55(6), 844–854. https://doi.org/10.1002/mnfr.201000641

Calderón-Montaño, J. M., Burgos-Morón, E., Pérez-Guerrero, C., & López-Lázaro, M. (2011). A review on the dietary flavonoid kaempferol. Mini reviews in medicinal chemistry, 11(4), 298–344. https://doi.org/10.2174/138955711795305335

Calixto, J. B., Santos, A. R., Cechinel Filho, V., & Yunes, R. A. (1998). A review of the plants of the genus Phyllanthus: their chemistry, pharmacology, and therapeutic potential. Medicinal research reviews, 18(4), 225–258. https://doi.org/10.1002/(sici)1098-1128(199807)18:4<225::aid-med2>3.0.co;2-x

Tena, N., Martín, J., & Asuero, A. G. (2020). State of the Art of Anthocyanins: Antioxidant Activity, Sources, Bioavailability, and Therapeutic Effect in Human Health. Antioxidants (Basel, Switzerland), 9(5), 451. https://doi.org/10.3390/antiox9050451

Liu, T., Liu, X., & Li, W. (2016). Tetrandrine, a Chinese plant-derived alkaloid, is a potential candidate for cancer chemotherapy. Oncotarget, 7(26), 40800–40815. https://doi.org/10.18632/oncotarget.8315

Cheng, C. L., Guo, J. S., Luk, J., & Koo, M. W. (2004). The healing effects of Centella extract and asiaticoside on acetic acid induced gastric ulcers in rats. Life sciences, 74(18), 2237–2249. https://doi.org/10.1016/j.lfs.2003.09.055

Li, X., Jiang, J., Yang, Z., Jin, S., Lu, X., & Qian, Y. (2021). Galangin suppresses RANKL-induced osteoclastogenesis via inhibiting MAPK and NF-κB signalling pathways. Journal of cellular and molecular medicine, 25(11), 4988–5000. https://doi.org/10.1111/jcmm.16430

Cicerale, S., Lucas, L. J., & Keast, R. S. (2012). Antimicrobial, antioxidant and anti-inflammatory phenolic activities in extra virgin olive oil. Current opinion in biotechnology, 23(2), 129–135. https://doi.org/10.1016/j.copbio.2011.09.006

Meng, S., Cao, J., Feng, Q., Peng, J., & Hu, Y. (2013). Roles of chlorogenic Acid on regulating glucose and lipids metabolism: a review. Evidence-based complementary and alternative medicine : eCAM, 2013, 801457. https://doi.org/10.1155/2013/801457

Dar, A., Faizi, S., Naqvi, S., Roome, T., Zikr-ur-Rehman, S., Ali, M., Firdous, S., & Moin, S. T. (2005). Analgesic and antioxidant activity of mangiferin and its derivatives: the structure activity relationship. Biological & pharmaceutical bulletin, 28(4), 596–600. https://doi.org/10.1248/bpb.28.596

Das, S., & Das, D. K. (2007). Resveratrol: a therapeutic promise for cardiovascular diseases. Recent patents on cardiovascular drug discovery, 2(2), 133–138. https://doi.org/10.2174/157489007780832560

Deschner, E. E., Ruperto, J., Wong, G., & Newmark, H. L. (1991). Quercetin and rutin as inhibitors of azoxymethanol-induced colonic neoplasia. Carcinogenesis, 12(7), 1193–1196. https://doi.org/10.1093/carcin/12.7.1193

Devi, P. U., Akagi, K., Ostapenko, V., Tanaka, Y., & Sugahara, T. (1996). Withaferin A: a new radiosensitizer from the Indian medicinal plant Withania somnifera. International journal of radiation biology, 69(2), 193–197. https://doi.org/10.1080/095530096146020

Dixon, R. A., & Ferreira, D. (2002). Genistein. Phytochemistry, 60(3), 205–211. https://doi.org/10.1016/s0031-9422(02)00116-4

Dugasani, S., Pichika, M. R., Nadarajah, V. D., Balijepalli, M. K., Tandra, S., & Korlakunta, J. N. (2010). Comparative antioxidant and anti-inflammatory effects of [6]-gingerol, [8]-gingerol, [10]-gingerol and [6]-shogaol. Journal of ethnopharmacology, 127(2), 515–520. https://doi.org/10.1016/j.jep.2009.10.004

Farah, A. and Donangelo, C.M. (2006) Phenolic Compounds in Coffee. Brazilian Journal of Plant Physiology, 18, 23-36.

https://doi.org/10.1590/S1677-04202006000100003

Fried, L. E., & Arbiser, J. L. (2009). Honokiol, a multifunctional antiangiogenic and antitumor agent. Antioxidants & redox signaling, 11(5), 1139–1148. https://doi.org/10.1089/ars.2009.2440

Zhu, X., Li, R., Wang, C., Zhou, S., Fan, Y., Ma, S., Gao, D., Gai, N., & Yang, J. (2021). Pinocembrin Inhibits the Proliferation and Metastasis of Breast Cancer via Suppression of the PI3K/AKT Signaling Pathway. Frontiers in oncology, 11, 661184. https://doi.org/10.3389/fonc.2021.661184

Fu, Y., Hsieh, T. C., Guo, J., Kunicki, J., Lee, M. Y., Darzynkiewicz, Z., & Wu, J. M. (2004). Licochalcone-A, a novel flavonoid isolated from licorice root (Glycyrrhiza glabra), causes G2 and late-G1 arrests in androgen-independent PC-3 prostate cancer cells. Biochemical and biophysical research communications, 322(1), 263–270. https://doi.org/10.1016/j.bbrc.2004.07.094

Lin, C., Liu, Z., Lu, Y., Yao, Y., Zhang, Y., Ma, Z., Kuai, M., Sun, X., Sun, S., Jing, Y., Yu, L., Li, Y., Zhang, Q., & Bian, H. (2016). Cardioprotective effect of Salvianolic acid B on acute myocardial infarction by promoting autophagy and neovascularization and inhibiting apoptosis. The Journal of pharmacy and pharmacology, 68(7), 941–952. https://doi.org/10.1111/jphp.12567

Gerhäuser C. (2005). Beer constituents as potential cancer chemopreventive agents. European journal of cancer (Oxford, England : 1990), 41(13), 1941–1954. https://doi.org/10.1016/j.ejca.2005.04.012

Gertsch, J., Leonti, M., Raduner, S., Racz, I., Chen, J. Z., Xie, X. Q., Altmann, K. H., Karsak, M., & Zimmer, A. (2008). Beta-caryophyllene is a dietary cannabinoid. Proceedings of the National Academy of Sciences of the United States of America, 105(26), 9099–9104. https://doi.org/10.1073/pnas.0803601105

Gil-Izquierdo, A., Gil, M. I., Ferreres, F., & Tomás-Barberán, F. A. (2001). In vitro availability of flavonoids and other phenolics in orange juice. Journal of agricultural and food chemistry, 49(2), 1035–1041. https://doi.org/10.1021/jf0000528

Harper P. (2023). A Review of the Dietary Intake, Bioavailability and Health Benefits of Ellagic Acid (EA) with a Primary Focus on Its Anti-Cancer Properties. Cureus, 15(8), e43156. https://doi.org/10.7759/cureus.43156

Gruenwald, J., Freder, J., & Armbruester, N. (2010). Cinnamon and health. Critical reviews in food science and nutrition, 50(9), 822–834. https://doi.org/10.1080/10408390902773052

Grzanna, R., Lindmark, L., & Frondoza, C. G. (2005). Ginger--an herbal medicinal product with broad anti-inflammatory actions. Journal of medicinal food, 8(2), 125–132. https://doi.org/10.1089/jmf.2005.8.125

Guerin, M., Huntley, M. E., & Olaizola, M. (2003). Haematococcus astaxanthin: applications for human health and nutrition. Trends in biotechnology, 21(5), 210–216. https://doi.org/10.1016/S0167-7799(03)00078-7

Gupta, S. C., Patchva, S., & Aggarwal, B. B. (2013). Therapeutic roles of curcumin: lessons learned from clinical trials. The AAPS journal, 15(1), 195–218. https://doi.org/10.1208/s12248-012-9432-8

Heumüller, S., Wind, S., Barbosa-Sicard, E., Schmidt, H. H., Busse, R., Schröder, K., & Brandes, R. P. (2008). Apocynin is not an inhibitor of vascular NADPH oxidases but an antioxidant. Hypertension (Dallas, Tex. : 1979), 51(2), 211–217. https://doi.org/10.1161/HYPERTENSIONAHA.107.100214

Hou, D. X., Fujii, M., Terahara, N., & Yoshimoto, M. (2004). Molecular Mechanisms Behind the Chemopreventive Effects of Anthocyanidins. Journal of biomedicine & biotechnology, 2004(5), 321–325. https://doi.org/10.1155/S1110724304403040

Sun, F., Xu, K., Zhou, J., Zhang, W., Duan, G., & Lei, M. (2023). Allicin protects against LPS-induced cardiomyocyte injury by activating Nrf2-HO-1 and inhibiting NLRP3 pathways. BMC cardiovascular disorders, 23(1), 410. https://doi.org/10.1186/s12872-023-03442-1

Wdowiak, K., Walkowiak, J., Pietrzak, R., Bazan-Woźniak, A., & Cielecka-Piontek, J. (2022). Bioavailability of Hesperidin and Its Aglycone Hesperetin-Compounds Found in Citrus Fruits as a Parameter Conditioning the Pro-Health Potential (Neuroprotective and Antidiabetic Activity)-Mini-Review. Nutrients, 14(13), 2647. https://doi.org/10.3390/nu14132647

Ge, L. N., Yan, L., Li, C., & Cheng, K. (2019). Bavachinin exhibits antitumor activity against non small cell lung cancer by targeting PPARγ. Molecular medicine reports, 20(3), 2805–2811. https://doi.org/10.3892/mmr.2019.10485

Jung, M., Triebel, S., Anke, T., Richling, E., & Erkel, G. (2009). Influence of apple polyphenols on inflammatory gene expression. Molecular nutrition & food research, 53(10), 1263–1280. https://doi.org/10.1002/mnfr.200800575

Motawea, M. H., Abd Elmaksoud, H. A., Elharrif, M. G., Desoky, A. A. E., & Ibrahimi, A. (2020). Evaluation of Anti-inflammatory and Antioxidant Profile of Oleuropein in Experimentally Induced Ulcerative Colitis. International journal of molecular and cellular medicine, 9(3), 224–233. https://doi.org/10.22088/IJMCM.BUMS.9.3.224

Irwin, J. J., Sterling, T., Mysinger, M. M., Bolstad, E. S., & Coleman, R. G. (2012). ZINC: a free tool to discover chemistry for biology. Journal of chemical information and modeling, 52(7), 1757–1768. https://doi.org/10.1021/ci3001277

Almeleebia, T. M., Alsayari, A., & Wahab, S. (2022). Pharmacological and Clinical Efficacy of Picrorhiza kurroa and Its Secondary Metabolites: A Comprehensive Review. Molecules (Basel, Switzerland), 27(23), 8316. https://doi.org/10.3390/molecules27238316

James, J. T., & Dubery, I. A. (2009). Pentacyclic triterpenoids from the medicinal herb, Centella asiatica (L.) Urban. Molecules (Basel, Switzerland), 14(10), 3922–3941. https://doi.org/10.3390/molecules14103922

Ruibin, J., Bo, J., Danying, W., Jianguo, F., & Linhui, G. (2020). Cardamonin induces G2/M phase arrest and apoptosis through inhibition of NF-κB and mTOR pathways in ovarian cancer. Aging, 12(24), 25730–25743. https://doi.org/10.18632/aging.104184

Chang, Y. L., Li, Y. F., Chou, C. H., Huang, L. C., Wu, Y. P., Kao, Y., & Tsai, C. K. (2021). Diosmin Inhibits Glioblastoma Growth through Inhibition of Autophagic Flux. International journal of molecular sciences, 22(19), 10453. https://doi.org/10.3390/ijms221910453

Huwait, E., & Mobashir, M. (2022). Potential and Therapeutic Roles of Diosmin in Human Diseases. Biomedicines, 10(5), 1076. https://doi.org/10.3390/biomedicines10051076

Kanehisa, M., Sato, Y., Furumichi, M., Morishima, K., & Tanabe, M. (2019). New approach for understanding genome variations in KEGG. Nucleic acids research, 47(D1), D590–D595. https://doi.org/10.1093/nar/gky962

Khan, N., & Mukhtar, H. (2007). Tea polyphenols for health promotion. Life sciences, 81(7), 519–533. https://doi.org/10.1016/j.lfs.2007.06.011

Khan, N., Syed, D. N., Ahmad, N., & Mukhtar, H. (2013). Fisetin: a dietary antioxidant for health promotion. Antioxidants & redox signaling, 19(2), 151–162. https://doi.org/10.1089/ars.2012.4901

Kim, S., Thiessen, P. A., Bolton, E. E., Chen, J., Fu, G., Gindulyte, A., Han, L., He, J., He, S., Shoemaker, B. A., Wang, J., Yu, B., Zhang, J., & Bryant, S. H. (2016). PubChem Substance and Compound databases. Nucleic acids research, 44(D1), D1202–D1213. https://doi.org/10.1093/nar/gkv951

El-Saber Batiha, G., Magdy Beshbishy, A., G Wasef, L., Elewa, Y. H. A., A Al-Sagan, A., Abd El-Hack, M. E., Taha, A. E., M Abd-Elhakim, Y., & Prasad Devkota, H. (2020). Chemical Constituents and Pharmacological Activities of Garlic (Allium sativum L.): A Review. Nutrients, 12(3), 872. https://doi.org/10.3390/nu12030872

Prajapati, R., Seong, S. H., Park, S. E., Paudel, P., Jung, H. A., & Choi, J. S. (2021). Isoliquiritigenin, a potent human monoamine oxidase inhibitor, modulates dopamine D1, D3, and vasopressin V1A receptors. Scientific reports, 11(1), 23528. https://doi.org/10.1038/s41598-021-02843-6

Lambert, J. D., & Yang, C. S. (2003). Mechanisms of cancer prevention by tea constituents. The Journal of nutrition, 133(10), 3262S–3267S. https://doi.org/10.1093/jn/133.10.3262S

Manu, K. A., Shanmugam, M. K., Rajendran, P., Li, F., Ramachandran, L., Hay, H. S., Kannaiyan, R., Swamy, S. N., Vali, S., Kapoor, S., Ramesh, B., Bist, P., Koay, E. S., Lim, L. H., Ahn, K. S., Kumar, A. P., & Sethi, G. (2011). Plumbagin inhibits invasion and migration of breast and gastric cancer cells by downregulating the expression of chemokine receptor CXCR4. Molecular cancer, 10, 107. https://doi.org/10.1186/1476-4598-10-107

Makabe, H., Maru, N., Kuwabara, A., Kamo, T., & Hirota, M. (2006). Anti-inflammatory sesquiterpenes from Curcuma zedoaria. Natural product research, 20(7), 680–685. https://doi.org/10.1080/14786410500462900

Shin, J. W., Lee, H. S., Na, J. I., Huh, C. H., Park, K. C., & Choi, H. R. (2020). Resveratrol Inhibits Particulate Matter-Induced Inflammatory Responses in Human Keratinocytes. International journal of molecular sciences, 21(10), 3446. https://doi.org/10.3390/ijms21103446

Ammon H. P. (2016). Boswellic Acids and Their Role in Chronic Inflammatory Diseases. Advances in experimental medicine and biology, 928, 291–327. https://doi.org/10.1007/978-3-319-41334-1_13

Malviya, S., Arvind, Jha, A., & Hettiarachchy, N. (2014). Antioxidant and antibacterial potential of pomegranate peel extracts. Journal of food science and technology, 51(12), 4132–4137. https://doi.org/10.1007/s13197-013-0956-4

Liu J. (2005). Oleanolic acid and ursolic acid: research perspectives. Journal of ethnopharmacology, 100(1-2), 92–94. https://doi.org/10.1016/j.jep.2005.05.024

Shen, J. L., Man, K. M., Huang, P. H., Chen, W. C., Chen, D. C., Cheng, Y. W., Liu, P. L., Chou, M. C., & Chen, Y. H. (2010). Honokiol and magnolol as multifunctional antioxidative molecules for dermatologic disorders. Molecules (Basel, Switzerland), 15(9), 6452–6465. https://doi.org/10.3390/molecules15096452

Li-Weber M. (2009). New therapeutic aspects of flavones: the anticancer properties of Scutellaria and its main active constituents Wogonin, Baicalein and Baicalin. Cancer treatment reviews, 35(1), 57–68. https://doi.org/10.1016/j.ctrv.2008.09.005

Lu, Y., & Foo, L. Y. (2002). Polyphenolics of Salvia--a review. Phytochemistry, 59(2), 117–140. https://doi.org/10.1016/s0031-9422(01)00415-0

Jiang, H., Qiu, J., Deng, X., Li, D., & Tao, T. (2023). Potential active compounds and common mechanisms of Evodia rutaecarpa for Alzheimer's disease comorbid pain by network pharmacology analysis. Heliyon, 9(8), e18455. https://doi.org/10.1016/j.heliyon.2023.e18455

Medzhitov R. (2010). Inflammation 2010: new adventures of an old flame. Cell, 140(6), 771–776. https://doi.org/10.1016/j.cell.2010.03.006

Naoe, A., Tsuchiya, T., Kondo, Y., Uga, N., Watanabe, S., Yasui, T., Hara, F., & Suzuki, T. (2019). Arctigenin induces apoptosis in human hepatoblastoma cells. Pediatric surgery international, 35(6), 723–728. https://doi.org/10.1007/s00383-019-04473-6

Mengoni, E. S., Vichera, G., Rigano, L. A., Rodriguez-Puebla, M. L., Galliano, S. R., Cafferata, E. E., Pivetta, O. H., Moreno, S., & Vojnov, A. A. (2011). Suppression of COX-2, IL-1β and TNF-α expression and leukocyte infiltration in inflamed skin by bioactive compounds from Rosmarinus officinalis L. Fitoterapia, 82(3), 414–421. https://doi.org/10.1016/j.fitote.2010.11.023

Nair, V., & Okello, M. (2015). Integrase Inhibitor Prodrugs: Approaches to Enhancing the Anti-HIV Activity of β-Diketo Acids. Molecules (Basel, Switzerland), 20(7), 12623–12651. https://doi.org/10.3390/molecules200712623

Pan, M. H., Lai, C. S., & Ho, C. T. (2010). Anti-inflammatory activity of natural dietary flavonoids. Food & function, 1(1), 15–31. https://doi.org/10.1039/c0fo00103a

Patel, D., Shukla, S., & Gupta, S. (2007). Apigenin and cancer chemoprevention: progress, potential and promise (review). International journal of oncology, 30(1), 233–245.

Petersen, M., & Simmonds, M. S. (2003). Rosmarinic acid. Phytochemistry, 62(2), 121–125. https://doi.org/10.1016/s0031-9422(02)00513-7

Pradhan, S. C., & Girish, C. (2006). Hepatoprotective herbal drug, silymarin from experimental pharmacology to clinical medicine. The Indian journal of medical research, 124(5), 491–504.

Miron, T., Rabinkov, A., Mirelman, D., Wilchek, M., & Weiner, L. (2000). The mode of action of allicin: its ready permeability through phospholipid membranes may contribute to its biological activity. Biochimica et biophysica acta, 1463(1), 20–30. https://doi.org/10.1016/s0005-2736(99)00174-1

Buhrmann, C., Mobasheri, A., Busch, F., Aldinger, C., Stahlmann, R., Montaseri, A., & Shakibaei, M. (2011). Curcumin modulates nuclear factor kappaB (NF-kappaB)-mediated inflammation in human tenocytes in vitro: role of the phosphatidylinositol 3-kinase/Akt pathway. The Journal of biological chemistry, 286(32), 28556–28566. https://doi.org/10.1074/jbc.M111.256180

Rao, A. V., & Agarwal, S. (2000). Role of antioxidant lycopene in cancer and heart disease. Journal of the American College of Nutrition, 19(5), 563–569. https://doi.org/10.1080/07315724.2000.10718953

Flythe, M. D., Kagan, I. A., Wang, Y., & Narvaez, N. (2017). Hops (Humulus lupulus L.) Bitter Acids: Modulation of Rumen Fermentation and Potential As an Alternative Growth Promoter. Frontiers in veterinary science, 4, 131. https://doi.org/10.3389/fvets.2017.00131

Rimando, A. M., Nagmani, R., Feller, D. R., & Yokoyama, W. (2005). Pterostilbene, a new agonist for the peroxisome proliferator-activated receptor alpha-isoform, lowers plasma lipoproteins and cholesterol in hypercholesterolemic hamsters. Journal of agricultural and food chemistry, 53(9), 3403–3407. https://doi.org/10.1021/jf0580364

Ross, J. A., & Kasum, C. M. (2002). Dietary flavonoids: bioavailability, metabolic effects, and safety. Annual review of nutrition, 22, 19–34. https://doi.org/10.1146/annurev.nutr.22.111401.144957

Nattagh-Eshtivani, E., Gheflati, A., Barghchi, H., Rahbarinejad, P., Hachem, K., Shalaby, M. N., Abdelbasset, W. K., Ranjbar, G., Olegovich Bokov, D., Rahimi, P., Gholizadeh Navashenaq, J., & Pahlavani, N. (2022). The role of Pycnogenol in the control of inflammation and oxidative stress in chronic diseases: Molecular aspects. Phytotherapy research : PTR, 36(6), 2352–2374. https://doi.org/10.1002/ptr.7454

Ru, J., Li, P., Wang, J., Zhou, W., Li, B., Huang, C., Li, P., Guo, Z., Tao, W., Yang, Y., Xu, X., Li, Y., Wang, Y., & Yang, L. (2014). TCMSP: a database of systems pharmacology for drug discovery from herbal medicines. Journal of cheminformatics, 6, 13. https://doi.org/10.1186/1758-2946-6-13

Russo, A., & Borrelli, F. (2005). Bacopa monniera, a reputed nootropic plant: an overview. Phytomedicine : international journal of phytotherapy and phytopharmacology, 12(4), 305–317. https://doi.org/10.1016/j.phymed.2003.12.008

Seelinger, G., Merfort, I., & Schempp, C. M. (2008). Anti-oxidant, anti-inflammatory and anti-allergic activities of luteolin. Planta medica, 74(14), 1667–1677. https://doi.org/10.1055/s-0028-1088314

Moon D. O. (2024). Curcumin in Cancer and Inflammation: An In-Depth Exploration of Molecular Interactions, Therapeutic Potentials, and the Role in Disease Management. International journal of molecular sciences, 25(5), 2911. https://doi.org/10.3390/ijms25052911

Chao, W. W., & Lin, B. F. (2010). Isolation and identification of bioactive compounds in Andrographis paniculata (Chuanxinlian). Chinese medicine, 5, 17. https://doi.org/10.1186/1749-8546-5-17

Shukla, S., & Gupta, S. (2010). Apigenin: a promising molecule for cancer prevention. Pharmaceutical research, 27(6), 962–978. https://doi.org/10.1007/s11095-010-0089-7

Srinivas, G., Babykutty, S., Sathiadevan, P. P., & Srinivas, P. (2007). Molecular mechanism of emodin action: transition from laxative ingredient to an antitumor agent. Medicinal research reviews, 27(5), 591–608. https://doi.org/10.1002/med.20095

Xiong, X., Tang, N., Lai, X., Zhang, J., Wen, W., Li, X., Li, A., Wu, Y., & Liu, Z. (2021). Insights Into Amentoflavone: A Natural Multifunctional Biflavonoid. Frontiers in pharmacology, 12, 768708. https://doi.org/10.3389/fphar.2021.768708

Zhang, J., Hunto, S. T., Yang, Y., Lee, J., & Cho, J. Y. (2020). Tabebuia impetiginosa: A Comprehensive Review on Traditional Uses, Phytochemistry, and Immunopharmacological Properties. Molecules (Basel, Switzerland), 25(18), 4294. https://doi.org/10.3390/molecules25184294

Szallasi, A., & Blumberg, P. M. (1999). Vanilloid (Capsaicin) receptors and mechanisms. Pharmacological reviews, 51(2), 159–212.

Szklarczyk, D., Gable, A. L., Lyon, D., Junge, A., Wyder, S., Huerta-Cepas, J., Simonovic, M., Doncheva, N. T., Morris, J. H., Bork, P., Jensen, L. J., & Mering, C. V. (2019). STRING v11: protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. Nucleic acids research, 47(D1), D607–D613. https://doi.org/10.1093/nar/gky1131

Tang, J., Feng, Y., Tsao, S., Wang, N., Curtain, R., & Wang, Y. (2009). Berberine and Coptidis rhizoma as novel antineoplastic agents: a review of traditional use and biomedical investigations. Journal of ethnopharmacology, 126(1), 5–17. https://doi.org/10.1016/j.jep.2009.08.009

Liudvytska, O., Bandyszewska, M., Skirecki, T., Krzyżanowska-Kowalczyk, J., Kowalczyk, M., & Kolodziejczyk-Czepas, J. (2023). Anti-inflammatory and antioxidant actions of extracts from Rheum rhaponticum and Rheum rhabarbarum in human blood plasma and cells in vitro. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie, 165, 115111. https://doi.org/10.1016/j.biopha.2023.115111

Idris, S., Mishra, A., & Khushtar, M. (2020). Phytochemical, ethanomedicinal and pharmacological applications of escin from Aesculus hippocastanum L. towards future medicine. Journal of basic and clinical physiology and pharmacology, 31(5), /j/jbcpp.2020.31.issue-5/jbcpp-2019-0115/jbcpp-2019-0115.xml. https://doi.org/10.1515/jbcpp-2019-0115

Wang, C. Z., Anderson, S., DU, W., He, T. C., & Yuan, C. S. (2016). Red ginseng and cancer treatment. Chinese journal of natural medicines, 14(1), 7–16. https://doi.org/10.3724/SP.J.1009.2016.00007

Jiang, W., Fu, F., Tian, J., Zhu, H., & Hou, J. (2011). Curculigoside A attenuates experimental cerebral ischemia injury in vitro and vivo. Neuroscience, 192, 572–579. https://doi.org/10.1016/j.neuroscience.2011.06.079

Woclawek-Potocka, I., Bah, M. M., Korzekwa, A., Piskula, M. K., Wiczkowski, W., Depta, A., & Skarzynski, D. J. (2005). Soybean-derived phytoestrogens regulate prostaglandin secretion in endometrium during cattle estrous cycle and early pregnancy. Experimental biology and medicine (Maywood, N.J.), 230(3), 189–199. https://doi.org/10.1177/153537020523000305

Woclawek-Potocka, I., Bah, M. M., Korzekwa, A., Piskula, M. K., Wiczkowski, W., Depta, A., & Skarzynski, D. J. (2005). Soybean-derived phytoestrogens regulate prostaglandin secretion in endometrium during cattle estrous cycle and early pregnancy. Experimental biology and medicine (Maywood, N.J.), 230(3), 189–199. https://doi.org/10.1177/153537020523000305

Woo, C. C., Kumar, A. P., Sethi, G., & Tan, K. H. (2012). Thymoquinone: potential cure for inflammatory disorders and cancer. Biochemical pharmacology, 83(4), 443–451. https://doi.org/10.1016/j.bcp.2011.09.029

Mohd Yusof Y. A. (2016). Gingerol and Its Role in Chronic Diseases. Advances in experimental medicine and biology, 929, 177–207. https://doi.org/10.1007/978-3-319-41342-6_8

Wu, W. H., Kang, Y. P., Wang, N. H., Jou, H. J., & Wang, T. A. (2006). Sesame ingestion affects sex hormones, antioxidant status, and blood lipids in postmenopausal women. The Journal of nutrition, 136(5), 1270–1275. https://doi.org/10.1093/jn/136.5.1270

Zhao, Q., Bi, Y., Guo, J., Liu, Y. X., Zhong, J., Pan, L. R., Tan, Y., & Yu, X. J. (2021). Pristimerin protects against inflammation and metabolic disorder in mice through inhibition of NLRP3 inflammasome activation. Acta pharmacologica Sinica, 42(6), 975–986. https://doi.org/10.1038/s41401-020-00527-x

Zeng, X., Zhang, P., He, W., Qin, C., Chen, S., Tao, L., Wang, Y., Tan, Y., Gao, D., Wang, B., Chen, Z., Chen, W., Jiang, Y. Y., & Chen, Y. Z. (2018). NPASS: natural product activity and species source database for natural product research, discovery and tool development. Nucleic acids research, 46(D1), D1217–D1222. https://doi.org/10.1093/nar/gkx1026

Yeo, S. C. M., Fenwick, P. S., Barnes, P. J., Lin, H. S., & Donnelly, L. E. (2017). Isorhapontigenin, a bioavailable dietary polyphenol, suppresses airway epithelial cell inflammation through a corticosteroid-independent mechanism. British journal of pharmacology, 174(13), 2043–2059. https://doi.org/10.1111/bph.13803

Ma, Z., Piao, T., Wang, Y., & Liu, J. (2015). Astragalin inhibits IL-1β-induced inflammatory mediators production in human osteoarthritis chondrocyte by inhibiting NF-κB and MAPK activation. International immunopharmacology, 25(1), 83–87. https://doi.org/10.1016/j.intimp.2015.01.018

Zhou, L., Zuo, Z., & Chow, M. S. (2005). Danshen: an overview of its chemistry, pharmacology, pharmacokinetics, and clinical use. Journal of clinical pharmacology, 45(12), 1345–1359. https://doi.org/10.1177/0091270005282630