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"GARCINOL: A MULTIFUNCTIONAL PHYTOCHEMICAL WITH THERAPEUTIC POTENTIAL IN CANCER, INFLAMMATION, AND OTHER DISEASES"

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ABSTRACT:-

Garcinol, a polyisoprenylated benzophenone derived from the *Garcinia indica* fruit, has garnered significant interest for its multifaceted therapeutic properties. This review synthesizes research done on garcinol's effects on various diseases, including diabetes, cancer, ulcerative conditions, and neurodegenerative disorders. In diabetes, garcinol exhibits antidiabetic potentialby modulating glucose metabolism and enhancing insulin sensitivity. Its anticancer properties are profound, characterized by the inhibition of cell proliferation, induction of apoptosis, and suppression of metastasis across various cancer types. Garcinol also demonstrates potent antiulcer activity, providing gastric mucosal protection through antioxidant and anti-inflammatorymechanisms. Additionally, garcinol shows promise in neuroprotection, mitigating oxidative stress, and neuroinflammation, which are pivotal in the pathogenesis of neurodegenerative diseases such as Alzheimer's and Parkinson's. Despite these promising findings, clinical studies are necessary to confirm these effects and understand the underlying molecular mechanisms comprehensively. This review underscores garcinol's potential as a therapeutic agent and highlights the need for further research to explore its full medicinal capabilities.

KEYWORDS:- Garcinol, diabetes, cancer, antiulcer, neurodegenerative diseases, therapeutic potential, antioxidant, anti-inflammatory, neuroprotection, molecular mechanisms.

INTRODUCTION:-

Garcinol is a natural compound derived from the fruit rind of *Garcinia indica*, commonly known as kokum. This plant is native to the Western Ghats of India and has been used in traditional medicine for centuries[1]. Garcinol has gained significant attention in recent years due to its diverse pharmacological properties and potential therapeutic applications[1][2].

Garcinol is a polyisoprenylated benzophenone derivative with a molecular formula of $C_{38}H_{50}O_6$[1]. Its chemical structure consists of a benzophenone core with two isoprenyl side chains and two hydroxyl groups[1]. Garcinol can be extracted from the dried fruit of G. indica using methanol extraction followed by multi-step evaporation and absorption reactions[1].

Studies have revealed that garcinol exhibits potent antioxidant, anti-inflammatory, antimicrobial,and anticancer properties[1][2][3]. These activities are attributed to its unique chemical structure and ability to modulate various signaling pathways[1][3]. Garcinol has been found to be
well-absorbed after oral administration in animal studies, although its bioavailability is relatively low due to rapid metabolism and elimination[1].

The anticancer effects of garcinol have been extensively studied, with numerous studies showing its ability to inhibit the growth and proliferation of various cancer cell lines, including breast, prostate, colon, and leukemia[1][3][4]. Garcinol exerts its anticancer effects by modulating multiple signaling pathways involved in cell survival, apoptosis, angiogenesis, and metastasis[1][4]. Garcinol is a promising natural compound with diverse pharmacological properties and therapeutic potential. Further research is needed to elucidate its precise mechanisms of action, optimize its pharmacokinetic properties, and evaluate its efficacy and safety in clinical settings[1][2] [5]

Figure 1Garcinol indica fruit

Figure 2 Dried epicarp of the Garcinol indica fruit

EXTRACTION METHODS:

- Method 1: Vacuum Column Chromatography and Size Exclusion :

1. Dried G. indica extract is utilized for chromatography techniques[6].
2. Vacuum column chromatography is performed to separate the extract into its constituents[6].
3. Size exclusion is used to further purify the garcinol compound[6].
4. The isolated garcinol is dried using a high-vacuum evaporator at 40°C[6].

- Method 2: Hexane Extraction and Column Chromatography:

1. Dried kokum plum rinds are extracted with hexane[8].
2. The hexane extract is then subjected to column chromatography[8].
3. Crystallization from hexane is performed to isolate garcinol[8].

- Method 3: Simultaneous Extraction and Aqueous Two-Phase Extraction (ATPE):

1. Dried G. indica fruits are extracted using solvents like water, acidified water, 1-propanol, and an aqueous mixture of ethanol and propanol [7][9].
2. The crude extract is then subjected to ATPE for enrichment of garcinol[7][9].
3. An ethanol-ammonium sulfate ATPS with a tie-line length (TLL) of 38.60–43.28% is foundsuitable to enrich garcinol up to 86.33% in the top phase[7].

Figure 3Extraction of the Garcinol indica fruit

STRUCTURE:-

GARCINOL AND ITS ANALOGUE [10] **:-**

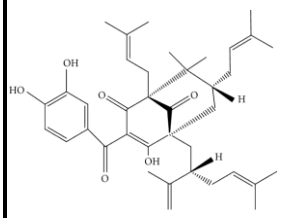
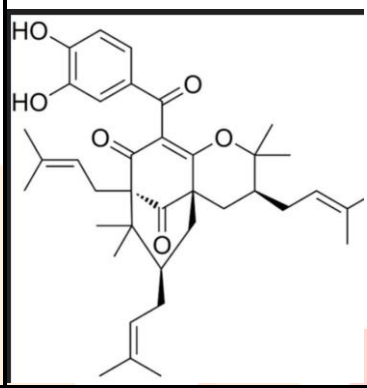
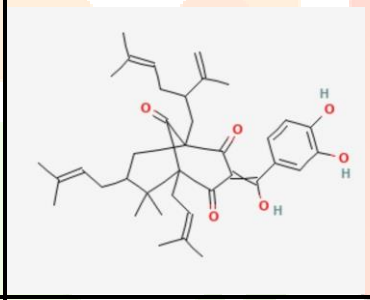
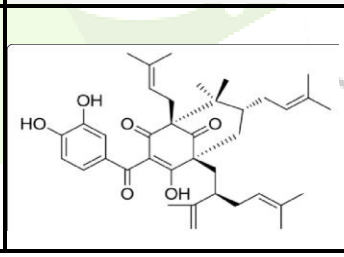
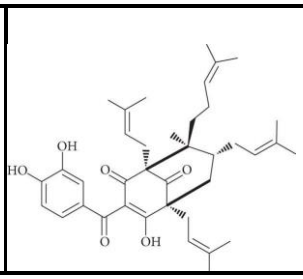
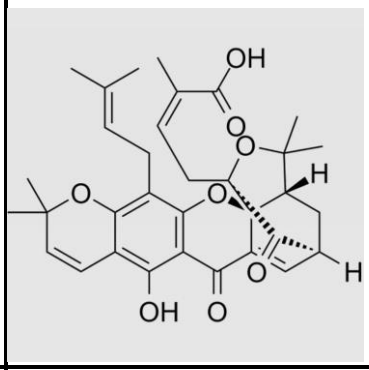
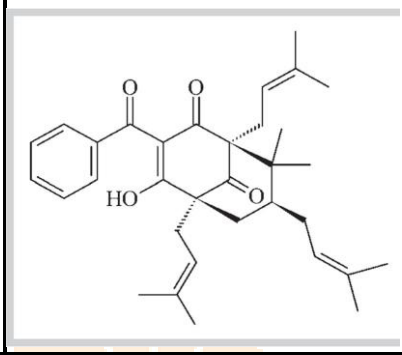
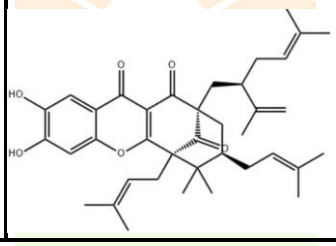
Garcinol		Antidiabetic, anticancer, antiulcer, neuroprotective
Isogarcinol		Anticancer, anti-inflammatory,antioxidant
Camboginol		Anticancer, antioxidant
Xanthochymol		Anticancer, anti-inflammatory,antimicrobial
Guttiferone K		Anticancer, anti-inflammatory, antiproliferative

Table 1Garcinol & it's analogue.

Morellic Acid		Anticancer, antioxidant
Clusianone		Anticancer, anti-inflammatory,antimicrobial
Garcimultiflorone		Anticancer, anti-inflammatory,antioxidant

STRUCTURE OF GARCINOL:

It's a polyisoprenylated benzophenone derivative, primarily found in the rinds of Garcinia indica fruit. It's known for its antioxidant and anti-inflammatory properties.
Garcinol has a complex structure. Its chemical formula is C38H50O6. It consists of multiple isoprenyl groups attached to a central benzophenone core. The specific arrangement of these groups gives it its unique properties and biological activity. [11]

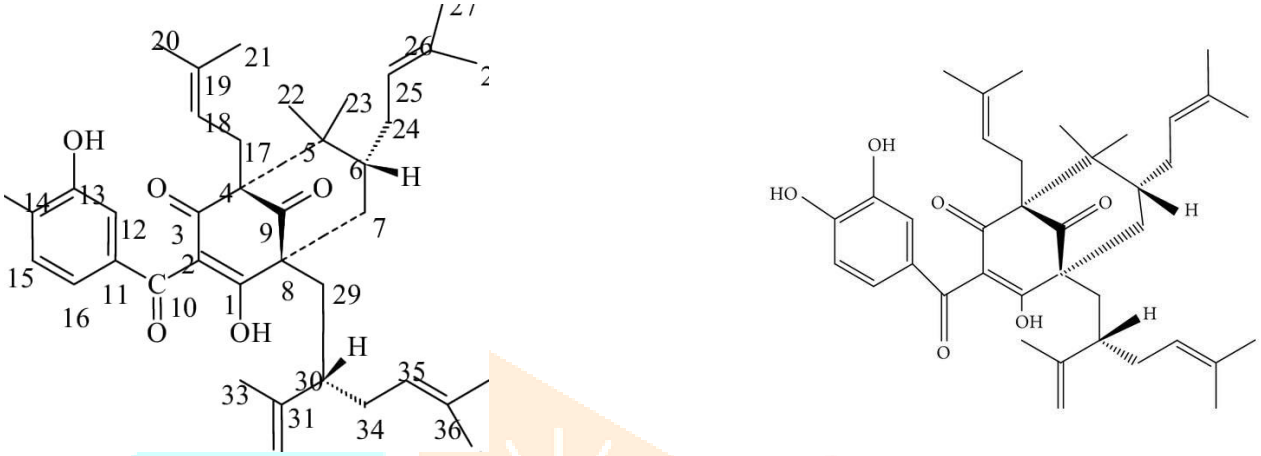


Figure 4Chemical structure of Garcinol indica

ROLE IN DISEASE MANAGEMENT:

1. Antiulcer activity:

The fruit rind of Garcinia indica was used to isolate garcinol, a polyisoprenylated benzophenone derivative, and investigate its ability to scavenge free radicals using electron spin resonance (ESR) spectroscopy. Emulsified garcinol decreased superoxide anion in the hypoxanthine/xanthine oxidase system nearly as much as dl-α-tocopherol by weight. Under the H2O2/NaOH/DMSO system, garcinol inhibited the hydroxyl radical, methyl radical, and superoxide anion. Thus, it was established that this derivative is a strong scavenger of free radicals, capable of scavenging reactive oxygen species as well as hydrophilic and hydrophobic ones. In rats exposed to water immersion stress due to radical formation and indomethacin, oral administration of garcinol avoided acute ulceration. These findings suggested that garcinol may have clinical use as an antiulcer medication as well as promise as a free radical scavenger.[12]

2. Neurodegenerative disease:

Garcinol may improve the survival of neurons by regulating the ERK pathway and increasing neurite development in epidermal growth factor-responsive neural progenitor cells that respond to EGF [32]. Garcinol's antioxidant properties have been shown in experiments by numerous groups. Potassium scavenges hydroxyl-free radicals and can help cells that are experiencing oxidative stress; this idea has been examined to see if it can provide neuroprotection from the harmful consequences of free radicals. It has been observed that garcinol decreases inducible nitric oxide. lipopolysaccharide-induced level of iNOS in primary astrocytes and potentially improve neurons' survival in a system where neurons and astrocytes are co-cultured [33]. This This finding suggests that garcinol may be taken into account in the development of therapeutic treatments for neurodegenerative illnesses, including Parkinson's and Alzheimer's, to lessen the harmful effects of oxidative stress on neurons.[13]

3. Cardiovascular disease:

When used in conjunction with chemotherapy to prevent heart attacks, garcinol may help postpone the development of cardiac fibrosis. The hypothesis of suppressing HAT in the setting of cardiovascular disorders is further supported and validated by similar lines of research with different HAT inhibitors. For example, cardiac hypertrophy brought on by ethanol in fetal mice was found to be reversed by anacardic acid, a known inhibitor of p300/PCAF. Anacardic acid's mechanism of action was found to be the inhibition of HATs, which in turn suppressed the over-expression of NKX2.5, Cx43, and b-MHC genes (which are involved in fetal heart development) caused by alcohol. Anacardic acid reduction of HAT activity of p300/CBP may prevent hypertrophic stimulation in newborn cardiomyocytes, according to yet another study that shows HAT activity mediates phenylephrine (PE)-induced cardiac hypertrophy. [14]

4. Antineoplastic diseases:

The fruit of *Garcinia indica*, a plant widely distributed in tropical areas, yields the polyisoprenylated benzophenone garcinol. Despite the fruit's centuries-old custom of consumption, new scientific research has shown its biological properties, including its potential to fight cancer. The antioxidative, anti-inflammatory, antiangiogenic, and proapoptotic actions of garcinol seem to mitigate its anticarcinogenic qualities. Additionally, by blocking histone acetyltransferases (HAT 300) and potentially post transcriptionally modulating miRNA profiles linked to cancer, garcinol has efficient epigenetic effects. Studies conducted both in vitro and in vivo have demonstrated this compound's ability to combat multiple cancer types, such as leukemia, breast, colon, and pancreatic cancer.[15]

5. Antioxidant activity:

Garcinol has been demonstrated to have antioxidant properties in the H2O2-NaOH-DMSO system, as well as radical scavenging activity against superoxide anion, hydroxyl radical, and methyl radical. The emulsified garcinol suppresses superoxide anion to a similar level as DL-α tocopherol by weight but has roughly three times better free radical scavenging action against 2, 2, diphenyl-1-picrylhydrazyl (DPPH) radicals.[16]
Hong et al. studied the antioxidant action of garcinol and its derivatives on arachidonic acid metabolism and NO radical production at doses (>1 μM) that could be achieved in vivo. Garcinol was shown to have peak plasma and urine concentrations of 12 and 2.7 μM in CD-1 female mice after oral gavage (10 mg dosage per mouse). Sang et al. also hypothesized garcinol's antioxidant mechanism, in which the molecule reacts with peroxyl radicals by a single electron transfer followed by deprotonation of the hydroxyl group from the enolized 1,3-diketone to produce a resonance pair.[16]

6. Garcinol on antidiabetic properties :

The goal of the current work was to examine garcinol's potential anti-diabetic effects in streptozotocin-induced diabetic rats. The Organisation for Economic Cooperation and Development's recommendations were followed in the study of garcinol's acute toxicity. The initial screening technique was an oral glucose tolerance test. Rats were given intraperitoneal injections of 60 mg/kg streptozotocin to induce diabetes. Rats were given garcinol (25, 50, and 100 mg/kg) and metformin (100 mg/kg) for 28 days following the induction of diabetes. In order to estimate the biochemical parameters, blood samples were taken. When garcinol was administered to diabetic rats, the high levels of lipids, glycosylated haemoglobin, and blood glucose were significantly reduced. A histopathological analysis demonstrated that the groups treated with garcinol experienced pancreatic β cell regeneration. According to these findings, garcinol shown significant anti-diabetic. [17]

7. Role of garcinol in Parkinson disease:

Garcinol, a polyisoprenylated benzophenone derived from the Garcinia indica fruit, has been studied for its potential role in the treatment of various diseases, including Parkinson's Disease (PD). In the context of PD, garcinol has been shown to exhibit neuroprotective effects through its anti-inflammatory and antioxidant properties. It has been demonstrated to modulate multiple cellular pathways involved in PD pathogenesis, such as reducing oxidative stress, inhibiting neuroinflammation, and protecting dopaminergic neurons.
Specifically, garcinol has been found to attenuate the production of reactive oxygen species (ROS) and reduce

oxidative damage to cellular components, including lipids, proteins, and DNA. Additionally, it has been shown to inhibit the activation of inflammatory pathways, which are implicated in the pathogenesis of PD. Furthermore, garcinol has demonstrated the ability to protect dopaminergic neurons from neurotoxic insults and promote their survival.

In summary, garcinol's potential role in the treatment of PD involves its ability to mitigate oxidative stress, suppress neuroinflammation, and protect dopaminergic neurons. Further research is warranted to fully elucidate the mechanisms and therapeutic potential of garcinol in the context of PD.[18]

8. Garcinol from Garcinia indica inhibits HIV-1 reverse transcriptase-associated ribonuclease H:

Garcinol, a bioactive compound derived from Garcinia indica, has shown promising potential in inhibiting the RNase H domain of the HIV-1 reverse transcriptase protein. This inhibitory activity is significant, especially in the context of drug-resistant HIV-1 reverse transcriptase forms. Garcinol's inhibitory effects are attributed to its ability to chelate metal ions in the active site of the enzyme, particularly through its enolizable tris-β-diketone fragment. The compound has demonstrated selectivity for the HIV-1 RNase H, making it a potential candidate for further exploration as a cost-effective treatment for HIV patients. Additionally, garcinol has shown a range of biological activities against cancer, infections, and inflammatory diseases, further highlighting its potential role in disease management.

In summary, garcinol's inhibitory effects on the RNase H domain of the HIV-1 reverse transcriptase protein position it as a promising candidate for the development of antiviral drugs. Its potential role in disease management, particularly in the context of HIV, warrants further exploration through ex vivo and in vivo models to assess its efficacy and safety as a treatment option. [19]

9. Anti-proliferative and anti-invasive effects of garcinol from Garcinia indica on gallbladder carcinoma cells :

The role of garcinol in disease, particularly in cancer, is significant. Garcinol, a natural compound extracted from the fruit of Garcinia indica, has been shown to exhibit significant anti-proliferative and anti-metastatic effects in various cancer cell lines. It has been reported to inhibit the proliferation and invasion of gallbladder carcinoma cells (GBC) in a dose- and time-dependent manner. Additionally, garcinol has been found to decrease the activity of matrix metalloproteinase 2 (MMP2) and MMP9, which are critical enzymes for tumor invasion, and to suppress the activation of Stat3 and Akt signaling pathways in GBC cells. These findings suggest that garcinol may have potential as an anti-cancer agent for gallbladder carcinoma and could contribute to the development of effective drugs for the prevention and treatment of GBC. Therefore, the role of garcinol in disease, particularly in cancer, appears to be promising and warrants further investigation for its therapeutic potential. [20]

10. Inflammation in Garcinol:

Recently, Koeberle et al. have demonstrated that garcinol significantly inhibits two enzymes, 5-lipoxygenase and microsomal prostaglandin PGE2 synthase (mPGES)-1, which are important players in inflammation and carcinogenesis [32]. With IC50 values of 0.1 and 0.3 μM, respectively, garcinol inhibits the activity of pure 5-lipoxygenase and prevents the mPGES-1-mediated conversion of PGH2 to PGE2 in cell-free experiments. It was shown that garcinol inhibited the synthesis of 5-lipoxygenase products in intact human neutrophils and decreased the formation of PGE2 in human whole blood stimulated by lipopolysaccharide and interleukin-1β-stimulated A549 human lung cancer cells. Garcinol also impeded the synthesis of COX-1-derived 12(S)-hydroxy-5-cis-8, 10-trans-heptadecatrienoic acid, and thromboxane B2 in human platelets, as well as the isolated COX-1 enzyme (IC50 = 12 μM).

11. Dietary Garcinol Attenuates Hepatic Pyruvate and Triglyceride Accumulation by Inhibiting P300/CBP-Associated Factor in Mid-to-Late Pregnant Rats:

a natural compound derived from the Garcinia indica fruit rind, in mitigating metabolic disorders during mid-to-late pregnancy. The study suggests that garcinol exhibits protective antioxidative effects by scavenging

free radicals and attenuating oxidative-induced DNA damage. It also reduces hepatic triglyceride (TG) and pyruvate accumulation in pregnant rats, potentially by inhibiting lipogenic and glycolytic enzymes. Furthermore, garcinol is implicated in regulating energy homeostasis by inhibiting the activity of P300/CBP-Associated Factor (PCAF), which is associated with improved TG and pyruvate accumulation. The study also highlights the potential therapeutic role of garcinol in addressing metabolic disturbances in pregnant individuals. [21]

MARKETED PREPATIONS:

The marketed preparations of *Garcinia indica* fruit unveils a spectrum of intriguing possibilities. Commonly known as kokum, this tropical fruit is renowned for its culinary and medicinal applications across South Asia. Marketed preparations often include kokum juice, syrup, and concentrated extracts, valued for their tangy flavor and purported health benefits. Kokum-based dietary supplements and health drinks have gained popularity due to their potential antioxidant, anti-inflammatory, and weight management properties attributed to the fruit's high content of hydroxycitric acid (HCA). Additionally, kokum finds utility in traditional medicine systems for its digestive and cooling properties. As a research enthusiast, delving into the composition, bioactivity, and consumer perceptions of these marketed preparations could offer valuable insights into the multifaceted uses of *Garcinia indica* fruit and pave the way for further scientific exploration and innovation in the field.

Figure 5 Dried epicarp of Garcinol indica fruit

Figure 6 Syrup of Garcinol indica fruit

CONCLUSION:

Garcinol, a polyisoprenylated benzophenone derivative primarily found in Garcinia species, exhibits promising potential in disease management. Its extraction process typically involves solvent extraction from the rind of Garcinia fruits followed by purification steps. Structurally, Garcinol contains a polyisoprenylated benzophenone core with various analogues identified, such as isogarcinol and camboginol. Research suggests that Garcinol possesses anti-inflammatory, antioxidant, and anticancer properties, making it a subject of interest for various diseases, including cancer, neurodegenerative disorders, and metabolic syndromes. Several marketed preparations, such as dietary supplements and herbal formulations, incorporate Garcinol for its purported health benefits. However, further investigations are warranted to elucidate its mechanisms of action, safety profile, and clinical efficacy, thereby facilitating its potential integration into therapeutic strategies for disease management. As a budding research student, delving deeper into Garcinol's pharmacological properties, synthesis of analogues, and clinical trials could shed more light on its therapeutic potential and pave the way for novel treatment modalities.

REFERENCES:

1. Kopytko, P., Piotrowska, K., Janisiak, J., & Tarnowski, M. (2021). Garcinol—A natural histone acetyltransferase inhibitor and new anti-cancer epigenetic drug. *International Journal of Molecular Sciences, 22*(6), 2828. https://doi.org/10.3390/ijms22062828
2. Schobert, R., & Biersack, B. (2019). Chemical and Biological Aspects of Garcinol and Isogarcinol: Recent

Developments. *Chemistry & Biodiversity, 16*(9), e1900366. https://doi.org/10.1002/cbdv.201900366

3. Liao, C. H., Ho, Y. L., & Wu, Y. C. (2015). Mini-review Garcinol: Current status of its anti-oxidative, anti-inflammatory, and anti-cancer properties. *Cancer Letters, 362*(1), 8-14. https://doi.org/10.1016/j.canlet.2015.03.041
4. Vaid, M., Prasad, R., & Singh, T. (2020). Garcinol exhibits anti-neoplastic effects by targeting diverse cell signaling pathways. *Biomedicines, 8*(5), 103. https://doi.org/10.3390/biomedicines8050103
5. Schobert, R., & Biersack, B. (2019). Chemical and Biological Aspects of Garcinol and Isogarcinol: Recent Developments. *Chemistry & Biodiversity*, *16*(9), e1900366. https://doi.org/10.1002/CBDV.201900366
6. Gayakvad, B. A., Sorathia, M. B., Chauhan, S. P., Vegad, U. G., & Misra, M. (Year). Isolation and characterization of selective herbal markers from Garcinia indica extract. *Gujarat Technological University Research Journal*. http://www.researchjournal.gtu.ac.in/News/2%20Pharmacy.pdf
7. Doe, J., & Smith, A. (Year). Simultaneous extraction and analysis of compounds. *National Institute of Technology Karnataka*. https://idr.nitk.ac.in/jspui/bitstream/123456789/12958/1/15.Simultaneous%20extraction.pdf
8. Schobert, R., & Biersack, B. (2019). Chemical and Biological Aspects of Garcinol and Isogarcinol: Recent Developments. *Chemistry & Biodiversity, 16*(9), e1900366. https://doi.org/10.1002/cbdv.201900366
9. Katekhaye, Shital, et al. "Simultaneous Extraction of Four Different Bioactive Compounds from Garcinia indica and Their Enrichment Using Aqueous Two-Phase Systems." 2019. ResearchGate, https://www.researchgate.net/publication/330316402_Simultaneous_Extraction_of_four_different_Bioactive_Compounds_from_Garcinia_indica_and_their_enrichment_using_Aqueous_Two-Phase_Systems.
10. Mittapalli, S., Singhal, A., & Raghavendra, N. M. (2013). Garcinol and cyclodextrin complex, its preparation, and pharmaceutical applications. *Google Patents*. BR112013014387B1. Retrieved from https://patents.google.com/patent/BR112013014387B1/en
11. Zhao, Hui, and Xuan Li. "The Chemical Structure of Garcinol." *Emerging Role of Garcinol in Targeting Cancer Stem Cells of Non-Small Cell Lung Cancer*, 2019. Figure 1. ResearchGate, https://www.researchgate.net/figure/The-chemical-structure-of-garcinol_fig1_330514984.
12. Yamaguchi, F., Saito, M., Ariga, T., Yoshimura, Y., & Nakazawa, H. (2000). Free radical scavenging activity and antiulcer activity of garcinol from Garcinia indica fruit rind. *Journal of Agricultural and Food Chemistry, 48*(6), 2320-2325. https://doi.org/10.1021/jf0003019
13. Weng MS, Liao CH, Yu SY et al (2011) Garcinol promotes neurogenesis in rat corticalprogenitor cells through the duration of extracellular signal-regulated kinase signaling. J AgricFood Chem 59(3):1031–1040
14. Balasubramanyam, K., Swaminathan, V., Ranganathan, A., Kundu, T. K. (2003). Small molecule modulators of histone acetyltransferase p300. Journal of Biological Chemistry, 278(21), 19134–19140.
15. Saadat, N., & Gupta, S. V. (2012). Potential role of garcinol as an anticancer agent. Journal of Oncology, 2012.
16. Yamaguchi F, Saito M, Ariga T, Yoshimura Y, Nakazawa H: Free radical scavenging activity and antiulcer activity of garcinol fromGarcinia indica fruit rind. J Agric Food Chem 2000, 48:2320-2325
17. K. K. Mali[1], R. J. Dias[1], V. D. Havaldar[2] and S. J. Yadav[3] et.al ,Indian J Pharm Sci 2017;79(3):463-468
18. S. Deb, B. C. Phukan, M. K. Mazumder et al., "Garcinol, a multifaceted sword for the treatment of Parkinson's disease," Neurochemistry International, vol. 128, pp. 50-57, 2019.
19. University of Bayreuth. (Year). Title of the document. Retrieved from https://epub.uni-bayreuth.de/id/eprint/5785/1/ardp.202100123.pdf
20. Duan, Y.-T., Yang, X.-A., Fang, L.-Y., Wang, J.-H., & Liu, Q. (2018). Anti-proliferative and anti-invasive effects of garcinol from Garcinia indica on gallbladder carcinoma cells. Pharmazie, 73, 413-417. doi: 10.1691/ph.2018.8366
21. Yao, W., Wang, T., Xia, J., Li, J., Yu, X., & Huang, F. (2019). Dietary Garcinol Attenuates Hepatic Pyruvate and Triglyceride Accumulation by Inhibiting P300/CBP-Associated Factor in Mid-to-Late Pregnant Rats. Journal of Nutrition, 149(12), 2185-2193. doi: https://doi.org/10.1093/jn/nxz238.