The natural polyisoprenylated benzophenone derivatives garcinol and isogarcinol are secondary plant metabolites isolated from various *Garcinia* species including *Garcinia indica*. This review takes stock of the recent chemical and biological research into these interesting natural compounds over the last five years. New biological sources and chemical syntheses are discussed followed by new insights into the activity of garcinol and isogarcinol against cancer, pathogenic bacteria, parasite infections and various inflammatory diseases.

**Keywords:** garcinol, isogarcinol, cancer, inflammation, infectious diseases.

### 1. Introduction

Natural products and their semi-synthetic derivatives occupy a salient position concerning activity and percentage share of new investigational and eventually approved drugs for the clinic.\(^\text{[1]}\) The traditional folk medicine of East Asia (Traditional Chinese Medicine, Kampo), South Asia (Ayurveda, Unani), the Middle-East (traditional Greco-Arab and Islamic Medicine) and other Asian regions, in particular, proved to be a valuable source of drug discovery based on natural products.\(^\text{[2,3]}\) In India, for example, plants or plant products from *Boswellia*, *Curcuma*, *Plumbago*, *Lawsonia*, and *Garcinia* among others, whose manifold activities were confirmed by modern laboratories meanwhile, have been applied by traditional healers until today.\(^\text{[4,5]}\) *Garcinia* species produce the biologically active benzophenones/polycyclic polyprenylated acylphloroglucinols (PPAPs) garcinol and isogarcinol which have raised the interest of chemists and molecular biologists alike (Figure 1).\(^\text{[6,7]}\) Garcinol is easily available in large amounts and high purity by extraction of dried kokum plums (*Garcinia indica*) followed by chromatographic purification and/or crystallization.\(^\text{[6,8]}\) Isogarcinol is easily prepared from garcinol by treatment with diluted hydrochloric acid.\(^\text{[9]}\) The activity spectra of garcinol and isogarcinol include anticancer, antibiotic, antioxidant and anti-inflammatory effects.\(^\text{[10]}\) Their modes of action are diverse and include the inhibition of NF-κB and STAT as well as of histone acetyl transferases (HATs).\(^\text{[11]}\) Several reviews and book chapters covered the extensive chemistry and biological activities of garcinol and isogarcinol over the last decade.\(^\text{[4,6,7,10,11]}\) The present review highlights the most recent proceedings in this field.

### 2. An Update on The Isolation, Analysis, and Synthesis of Garcinol and Isogarcinol

Garcinol and isogarcinol were isolated from various *Garcinia* species. High yields of garcinol can be obtained from dried kokum (*Garcinia indica*) plums while garcinol can be easily converted to isogarcinol under acidic conditions.\(^\text{[6,8]}\) High yields of garcinol (up to 5 g from 500 g dried kokum plums) were achieved...
by extraction of chopped dried kokum plums with methanol, evaporation of the solvent, redissolution of the methanol extract in ethyl acetate, washing of the latter with water, column chromatography of the concentrated ethyl acetate extract (silica gel 60, ethyl acetate/hexane 1:2) followed by crystallization of the concentrated eluate from hexane to give yellow needles. \[2\] Isogarcinol can be easily prepared by treatment of garcinol with aqueous HCl in toluene at room temperature. \[6\] Another suitable large scale isolation method initially removed hydroxycitric acid from \textit{Garcinia indica} fruits by washing with water, followed by methanol extraction of the fruits, adsorption of the concentrated methanol extract on Celite and extraction of the methanol extract loaded Celite with hexane followed by column chromatography of the hexane extract. \[8\] Recently, garcinol and isogarcinol were isolated from fruits of \textit{Garcinia multiflora}, a medicinal plant of South China known for its antioxidant activity. \[10,12\] The authors obtained 500 mg garcinol and 101 mg isogarcinol from 5.2 kg dried \textit{G. multiflora} fruits (powdered dried \textit{G. multiflora} fruits were extracted with 95% ethanol and the ethanol extract was extracted with petroleum ether followed by column chromatography on silica gel and recrystallization to obtain garcinol). \[12\] Garcinol was also detected in and isolated from plants of the \textit{Garcinia} species \textit{G. morella}, \textit{G. yunnanensis}, \textit{G. xanthochymus} and \textit{G. travancorica}. \[13 – 16\] In addition, garcinol and isogarcinol were recently found in the stem bark of the \textit{Garcinia} species \textit{G. buchananii}. \[17\] Isogarcinol was also isolated from \textit{G. punctata} and \textit{G. ovalifolia}. \[18,19\]

Quantitative analyses of garcinol contents in biological material are usually carried out by LC/MS and HPLC methods. \[20 – 22\] Recently, the garcinol contents of \textit{Garcinia indica} samples and of the commercially available formulations Tryodashang Guggul and Slimmerz capsules was determined by High Performance Thin Layer Chromatography (HPTLC). It was shown that the dried fruit rinds of \textit{Garcinia indica} contained 2.5% garcinol while Tryodashang Guggul had 0.701% and Slimmerz capsules 0.760% garcinol. \[23\] With aqueous two-phase systems (ATPS) containing ethanol and ammonium sulfate garcinol and isogarcinol accumulated in the ethanol phase while anthocyanin and hydroxycitrate built up in the salt-rich phase. \[24\] Gold nanoparticles (AuNPs), prepared from \textit{G. indica} fruit rind extract, showed distinct catalytic activities such as a reduction of toxic 4-nitrophenol to 4-aminophenol when combined with NaBH₄. \[25\]

Distinct progress has also been achieved in the field of the total synthesis of garcinol and isogarcinol. Socolsky and Plietker described a concise total synthesis of racemic garcinol and isogarcinol in 13 steps starting from acetylaceitone, which was \(\alpha\)-prenylated and reacted with formaldehyde via deacetylation aldol-type condensation to give enone 1 (Scheme 1). The latter was submitted to a domino Michael addition–Knoevenagel condensation with dimethyl 1,3-acetonedicarboxylate to afford the cyclohexanone hub of intermediates 2 and 3. Allylation of the keto ester 3 with 4-acetoxypropyl chloride gave trans-selectively 4, which was \(\beta\)-methylated and O-alloc protected to furnish enol allyl carbonates 5a and 5b. Both regioisomers 5 underwent a carboxylative, dia-stereoselective, Pd-catalyzed Tsuji–Trost allylation yielding the same cyclohexanone 6. Its subsequent Pd-catalyzed allyl-allyl cross-coupling with allylpinacolborane afforded exclusively the 1,5-dienyl derivative 7, which was submitted to a Dieckmann condensation.
leaving bicyclo[3.3.1]nonatriene 8. Its cross-metathesis with amylene to introduce the prenyl residues, followed by benzoylation and deprotection finally yielded the natural product garcinol.\[26\]

3. An Update on The Activities of Garcinol and Isogarcinol against Tumor Models

The significant activity of garcinol and isogarcinol against various tumor models is largely attributed to the inhibition of histone acetyl transferases (HATs), NF-κB signaling, and STAT-signaling. Meanwhile, new promising results were disclosed (Table 1).

Lung cancer is one of the most lethal cancers and leads annually to ca. 1.2 million deaths worldwide.\[27\] Non-small cell lung cancer cells were sensitized to cisplatin and erlotinib treatment by garcinol. This effect was mediated by miRNAs and garcinol was able to upregulate EMT-modulating miRNAs such as let-7c and miR-200b.\[28\] Lung cancer stem cells (LCSCs) were also targeted by garcinol and repression of the Wnt/β-catenin/STAT3 signaling pathway by garcinol treatment suppressed the ability of NSCLC cells to form...
Table 1. Recently discovered antitumor effects of garcinol and isogarcinol.

| Cancer type           | Effects                                                                 | Mechanisms                                                                 | In vivo activity                                      |
|-----------------------|------------------------------------------------------------------------|---------------------------------------------------------------------------|-------------------------------------------------------|
| Lung cancer           | Sensitization to cisplatin and erlotinib (garcinol), suppression of cancer stem cells (garcinol), increased TRAIL-based apoptosis (garcinol) | Upregulation of let-7c and miR-200c (garcinol), suppression of Wnt/β-catenin/STAT3 and ALDH1 A1 (garcinol), activation of DDIT3, induction of DR5 (garcinol), suppression of c-FLIP (garcinol) | Inhibition of H441 LCSC mouse xenograft tumor growth (garcinol) |
| Colorectal cancer     | Increased apoptosis and cell growth inhibition (garcinol), inhibition of angiogenesis and invasion (garcinol), decreased tumor growth in H441 LCSC mouse xenograft model. | Suppression of mPGES1, HIF-1α, VEGF, MMP (garcinol), inhibition of base excision repair via HAT inhibition (garcinol) | -                                                      |
| Breast cancer         | Sensitization to taxol (garcinol), increased apoptosis (garcinol)       | Suppression of caspase-3/PLA2 and NF-κB/Twist1 signaling (garcinol), p53 dependent induction of Bax (garcinol), suppression of Bcl-XL (garcinol), proteasome-based degradation of ADA3 (garcinol) | Sensitization to taxol in orthotopic 4T1 mammary carcinoma (garcinol) |
| Prostate cancer       | Increased apoptosis, inhibition of autophagy (garcinol)                 | Induction of Bax, suppression of Bcl-2 and mTOR (garcinol)                | Inhibition of PC-3 mouse xenograft tumor growth (garcinol) |
| Pancreatic cancer     | Suppression of cancer stem cell characteristics (garcinol), tumor growth inhibition (garcinol) | Suppression of Mcl-1, EZH2, ABCG2, Gli-1, and Notch-1, induction of miR-200c (garcinol) | Inhibition of tumor growth in KPC mice: K-ras and p53 conditional mutant mice (garcinol) |
| Oral squamous cell carcinoma | Inhibition of tumor cell growth, induction of apoptosis, inhibition of angiogenesis and colony formation (garcinol) | | -                                                      |
| Cervical cancer       | Inhibition of tumor cell growth (garcinol), suppression of tumorigenesis (garcinol), sensitization to radiotherapy (garcinol) | Activation of PI3 K/AKT signaling (garcinol), suppression of HIF-1α (garcinol) | Induction of T-cadherin in vivo (garcinol) |
| Miscellaneous cancers | Tumor cell growth inhibition (gallbladder carcinoma (garcinol), neuroblastoma (garcinol), melanoma (GARNPs), hepatoma (GARNPs), leukemia (isogarcinol), synergy with STAT5-SH2 domain inhibitor AC-4-130 (leukemia, garcinol), induction of apoptosis and G2/M arrest (leukemia, isogarcinol), induction of autophagy (osteosarcoma, garcinol) | Suppression MMP2 and MMP9 (gallbladder carcinoma (garcinol), synergy with STAT5 inhibition via HAT inhibition (leukemia, garcinol), increased TRAIL-based apoptosis by induction of DR5 and suppression of c-FLIP (hepatoma, renal cancer, garcinol), LC-3 shift (osteosarcoma, garcinol) | Moderate accumulation of garcinol nanoparticles in tumors of B16-F10 tumor bearing mice (GARNPs) |

Garcinol sensitized CRC and breast cancer cells to treatment with taxol in vitro and in vivo. The synergistic effect of garcinol with taxol on tumor growth inhibition and anti-metastatic activity was observed in orthotopic 4T1 mammary carcinoma. Resistance to chemotherapy is a big problem. Garcinol was able to sensitize breast tumors to treatment with taxol in vivo (orthotopic 4T1 mammary carcinoma). Synergistic tumor growth inhibition and anti-metastatic activity were observed in breast cancer xenografts. Garcinol was able to sensitize breast tumors to treatment with taxol in vivo (orthotopic 4T1 mammary carcinoma). Synergistic tumor growth inhibition and anti-metastatic activity were observed in breast cancer xenografts.
for this promising drug combination at low doses (1 mg/ kg garcinol orally three times per week + 5 mg/ kg taxol i.p. once per week) attributable to the downregulation of caspase-3/iPLA2 and NF-κB/Twist1 signaling.\[36\] The chloroform extract of G. morella rich in bioactive garcinol exhibited distinct growth inhibitory effects against three breast cancer cell lines (MCF-7, MDA-MB-231, SKBR3). MCF-7 cells treated with the G. morella chloroform extract revealed increased apoptosis levels by p53 dependent induction of Bax and suppression of Bcl-XL.\[13\]

In the Western world prostate cancer is the second most frequent cause of cancer-related death after lung carcinoma.\[37\] In PC-3 prostate carcinoma cells, garcinol induced apoptosis by induction of Bax and suppression of Bcl-2 as well as by inhibition of autophagy via activating phosphorylation of mTOR. Garcinol (50 mg/kg five times per week for 40–50 days, i.p. or orally) also inhibited tumor growth of PC-3 mouse xenografts by 80%.\[38\]

Individuals diagnosed with pancreatic cancer (PC) still face a poor prognosis.\[39\] The high incidence of resistance and metastasis of pancreatic cancer was correlated to the presence of cancer stem-like cells that are also called side population (SP) cells. Garcinol suppressed the stem cell character of Panc-1 SP cells by inhibition of crucial SP-related factors such as Mcl-1, EZH2, ABCG2, Gl-1, and Notch-1. In addition, upregulation of the tumor suppressor microRNA miR-200c (target: Notch-1) was observed upon garcinol treatment.\[40\] In transgenic PC mice (KPC mice: K-ras and p53 conditional mutant mice), garcinol and the combination of a garcinol diet with injected gemcitabine inhibited tumor growth.\[41\]

With more than 300,000 people suffering from oral squamous cell carcinoma (OSCC) every year all over the world, this malignancy is the sixth most common tumor disease and many cases go on developing without treatment.\[42\] Garcinol inhibited the tumor cell growth of the OSCC cell lines SCC-4, SCC-9 and SCC-25 in vitro (IC50 = 5–15 μM), induced apoptosis in these cancer cells, blocked angiogenesis and reduced significantly the number of formed colonies by SCC-4 and SCC-9 cells. Inhibition of NF-κB and of COX-2 as well as suppression of VEGF were identified as modes of action of garcinol in these OSCC cells.\[43\] The chemical modification of garcinol allowed insights into the importance of functional groups of this compound concerning activity against tumor models. For instance, the 13,14-dihydroxy groups proved essential for the activity of garcinol because their methyl ethers exhibited weaker activity against SCC15 OSCC cells.\[44\]

The total synthesis and testing of an 8-methyl garcinol derivative showed the high importance of the 8-prenyl group of natural garcinol for activity against SCC15 cells.\[45\] In contrast, the synthetic 8-allyl garcinol derivative displayed a strong growth inhibition of oral cancer cells.\[46\]

Cervical carcinoma (CC) is the cause of death of 300,000 women globally every year and patients with metastases and suffering from relapse have a poor prognosis.\[47\] Garcinol showed activity against CC models. Tumorigenesis of CC was correlated with T-cadherin expression and garcinol induced T-cadherin in vitro and in vivo via activation of PI3 K/AKT signaling in CC.\[48\] Radiation therapy is customarily applied for CC patients and, thus, it is interesting to note that garcinol increased the sensitivity of oxygen-deficient HeLa CC cells to radiation by suppression of HIF-1α.\[49\]

In addition, the effects of garcinol and isogarcinol were studied in various other cancers. Garcinol inhibited gallbladder carcinoma (GBC) cell growth and cell invasion by suppression of the matrix metalloproteinases MMP2 and MMP9. Both STAT3 and Akt were downregulated by garcinol in GBC-SD cells.\[50\]

Garcinol and the chloroform extract of G. morella inhibited the growth of the childhood tumor and neuroblastoma cell line SH-SYSY (IC50 = 6.3 μM for garcinol).\[51\] Both garcinol and isogarcinol displayed activities against leukemia models. The STAT5-SH2 domain inhibitor AC-4-130 showed strongly synergistic effects against acute myeloid leukemia (AML) cells MV4-11 and MOLM-13 in combination with the HAT inhibitor garcinol probably because acetylation of STAT5 by the HATs p300 and PCAF is of importance for the regulation of STAT5 phosphorylation/dimerisation.\[52\]

Isogarcinol isolated from G. ovalifolia roots exhibited distinct activity against HL-60 promyelocytic leukemia cells (IC50 = 4 μg/mL) and induced G2/M arrest as well as apoptosis via mitochondrial damage in these leukemia cells.\[19\] While garcinol is only poorly soluble in water, PLGA nanoparticles modified with vitamin E as carriers of garcinol (GAR-NPs) revealed significant growth inhibitory activities against B16-F10 melanoma, HepG2 hepatocellular carcinoma, and KB cervical carcinoma cells. The GAR-NPs showed improved uptake rates, time-dependent accumulation in B16-F10 tumor bearing mice as well as apoptosis induction.\[53\]

New discoveries concerning mechanisms of action of garcinol and isogarcinol in tumor models were disclosed. In hepatoma (SK-Hep1), lung (A549) and renal carcinoma cells (Caki, ACHN, A498) garcinol increased TRAIL-based apoptosis by induction of DR5.
and suppression of c-FLIP.\textsuperscript{[54]} The HAT inhibitor garcinol also led to proteasome-based degradation of the factor ADA3 (alteration/deficiency in activation 3) in immortalized 76 N-TERT cells (human mammary epithelial cells) by inhibition of stabilizing ADA3 acetylation \textit{via} p300/PCAF inactivation.\textsuperscript{[55]} In this way, garcinol may show synergistic effects in combination with EGFR inhibitors. In U2OS osteosarcoma cells garcinol induced autophagy and a correlated LC3-shift by inhibition of EP300 (E1 A-binding protein p300).\textsuperscript{[56]} The HAT BRD4 (bromodomain protein 4) enhanced the transcription of target genes such as MYC, FOS and AURKB (Aurora kinase B) but BRD4 was efficiently inhibited by garcinol while another pan-inhibitor (curcumin) displayed no BRD4 inhibitory effects.\textsuperscript{[57]} Hence, BRD4 inhibition can contribute to the activity of garcinol. Garcinol was described as a time- and detergent-dependent inhibitor of lysine acetyltransferases (KATs, a more specific name for HATs). High Triton-X-100 concentrations (0.05\%) reduced the KAT-inhibitory activity of garcinol for p300 and GCN5 KATs when compared with experiments using low Triton-X-100 concentrations (0.01\%), which is of great importance for future biological tests with garcinol in order to obtain reasonable results.\textsuperscript{[58]} Because of these findings an aggregation-based mode of KAT inhibition was suggested for garcinol. Based on the lead compound garcinol, a synthetic and non-competitive, selective and reversible inhibitor (EML245) of the KAT3 enzymes p300 (IC\textsubscript{50} = 2.9 \textmu M) and CBP (IC\textsubscript{50} = 1.1 \textmu M) was obtained. EML245 showed significant cell permeation and reduced lysine H4 K5 and H3 K9 acetylation in U937 leukemia cells leading to G0/G1 arrest and formation of hypodiploid nuclei.\textsuperscript{[59]}

### 4. An Update on The Activities of Garcinol against Viruses, Bacteria, Yeasts, and Protozoal Parasites

Garcinol has shown promising activity against causing agents and consequences of various infectious diseases. \textit{Table 2} summarizes a few of the more interesting findings.

As early as 2007, the suppression of viral transcription by HIV was documented for isogarcinol derivatives as well as their p300 inhibitory activity.\textsuperscript{[60]} Recently, a similar mode of action against the influenza virus was reported of garcinol. Garcinol inhibited both PCAF (p300/CBP-associated factor) and GCN5 in influenza A leading to a reduced acetylation of the viral nucleoprotein and to the regulation of the viral polymerase function. Interestingly, both HATs target different lysines of the nucleoprotein: while PCAF acetylate Lys-31, GCN5 acetylates Lys 90. Both lysines regulate opposite effects: deacetylated Lys-31 PCAF acetylate Lys-31, GCN5 acetylates Lys 90. Both target different lysines of the nucleoprotein: while

| Infection | Effects | Mechanisms |
|-----------|---------|------------|
| Influenza A\textsuperscript{[61]} | Regulation of viral polymerase function | Inhibition of PCAF and GCN5 |
| Bacillus anthracis\textsuperscript{[62]} | Antidote for LT intoxication | Reduction of stress-fiber formation |
| Candida albicans\textsuperscript{[15]} | Induction of apoptosis, inhibition of biofilm formation | Inhibition of TgGCN5b |
| Toxoplasma gondii\textsuperscript{[63]} | Inhibition of replication | |

The lethal toxin (LT) of the Gram-positive bacterium \textit{Bacillus anthracis} induces actin stress fiber formation in infected cells by suppression of HDAC expression and, thus, this process is controlled by histone acetylation. In contrast to LT, the HAT inhibitor garcinol reduced stress fiber formation in LT-treated HUVEC cells and so might act as an antidote for LT intoxication.\textsuperscript{[62]}

The activity of garcinol against cells of the pathogenic fungus \textit{Candida albicans} was studied as well. Garcinol and xanthochymol induced apoptosis in \textit{C. albicans} hyphae and inhibited biofilm production by this fungus.\textsuperscript{[15]}

The viability of \textit{Toxoplasma gondii}, which is a protozoal parasite causing toxoplasmosis, is regulated by lysine acetylation. The GCN5 family KAT TgGCN5b of \textit{T. gondii} is crucial for replication of the \textit{T. gondii} tachyzoites. Garcinol treatment led to decreased levels of acetylated histone H3 of TgGCN5b and to an inhibition of replication (IC\textsubscript{50} = 1.7 \textmu M). Similar replication inhibitory effects were observed for the malaria parasite \textit{Plasmodium falciparum} (IC\textsubscript{50} = 1.69 \textmu M for chloroquine-sensitive HB3 strains, and IC\textsubscript{50} = 2.05 \textmu M for chloroquine-resistant Dd2 strains; inhibition of erythrocytic asexual replication).\textsuperscript{[63]}

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Table 3. Recently discovered effects of garcinol and isogarcinol on inflammation and neurodegenerative diseases.

| Disease                                      | Effects                                                                 | Mechanisms                                                                 |
|----------------------------------------------|------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Skin inflammation                            | Inhibition of 12-0-tetradecanoylphorbol induced inflammation process and tumorigenesis in vitro and in vivo[65]^6   | Suppression of NF-κB, ERK, JNK, p38 MAPK, PI3 K, and Akt[65]                |
| Intimal hyperplasia                          | Suppression of leukocyte and vascular smooth muscle cell inflammation process in vitro, reduced arterial adherence and infiltration by leukocytes and macrophages in vivo[66] | Suppression of CCL2 and TNF-α[66]                                          |
| LPS-induced inflammation                     | Increase of LPS-induced inflammation process in vitro and in vivo[67]   | Increased expression of TNF-α and IL-6[67]                                 |
| Collagen-induced arthritis (CIA)             | Suppression of CIA and ear edema, reduced bone and cartilage damage and low concentrations of inflammatory cytokines in vivo[68] | Suppression of NF-κB, iNOS, COX-2, NFAT and IL-2[68]                        |
| Systemic lupus erythematosus (SLE) disease   | Protection of kidneys in vivo, reduced renal histopathology and proteinuria, normalized serum biochemical indicator[69] | Suppression of IL-23/Th17 axis genes[70]                                    |
| Psoriasis                                    | Amendment of skin lesions induced by imiquimod, less toxic to liver and kidneys than cyclosporine A in vivo[70] | Suppression of collagenase, elastase and hyaluronidase excretion[71]       |
| Macrophages                                  | Beneficial effects on macrophages and peritoneal macrophages, reduced excretion of lysosomal enzymes in vivo[71] | Suppression of histone acetylation[73]                                    |
| Liver inflammation and acute liver failure   | Prolonged survival of mice with acute liver failure[71] | Restoration of transcription factor KLF11 function, suppression of scar-tissue collagen (COL1 A1/Col11a1)[74] |
| Endometriosis                                | Suppression of fibrosis in Klf11^-/-^ animals[74] | Suppression of PI3 K/Akt, MAPK and NF-κB signaling[79] | Targeting of JAK/STAT signaling pathway[80] |
| Obesity-related inflammation                 | Inhibition of high fat diet (HFD)-induced obesity in vivo[75]           | Increased levels of intestinal commensal bacteria Akkermansia, suppression of glutamate pyruvate transaminase, cholesterol and triacylglycerol[73] |
| Diabetes                                     | Normalization of diabetic parameters in vivo[77]                        | Suppression of PI3 K/Akt, MAPK and NF-κB signaling[79] | Targeting of JAK/STAT signaling pathway[80] |
| Osteolysis                                   | Suppression of osteoclastogenesis in vivo[79]                          | Suppression of histone acetylation[73]                                    |
| Multiple sclerosis, experimental autoimmune encephalomyelitis | Reduced intracranial lesions and demyelination of the spinal cord in vivo[80] | Suppression of acetyl-p65[81]^81 downregulation of NF-κB signaling, reduced expression of COX-2/PGE2, iNOS and interleukins (IL-1b, IL-6)[82] |
| Neuroinflammation of microglia               | Prolonged thermal withdrawal latency[82]                                | Suppression of acetyl-p65[81]^81 downregulation of NF-κB signaling, reduced expression of COX-2/PGE2, iNOS and interleukins (IL-1b, IL-6)[82] |
| Parkinson’s disease                          | Neuroprotective effects[83]^83 reduction of dopamine side-effects/dyskinesia[84,85] | MAO–B inhibition[83]^83 inhibition of catechol-O-methyltransferase[85] |
| Epilepsy                                     | Decrease of mortality and of seizure scores in vivo[86]                | Suppression of BDNF and TrkB and upregulation of GABA_A and GAD65[86] |
| Cocaine abuse                                | Support of drug abstinence[87,88]                                        | Inhibition of reinstatement by reconsolidation-based modes[85,88]          |

5. New Effects on Inflammation Processes and Neurodegenerative Diseases

The antioxidant and anti-inflammatory properties of garcinol and isogarcinol are well described (Table 3).[10]

Only recently, isogarcinol was reported to have significant antioxidant effects rescuing human cells from oxidative stress while the genotoxicity of isogarcinol was negligible.[64] Topically applied garcinol efficiently blocked skin inflammation and tumorigenesis induced by 12-O-tetradecanoylphorbol 13-acetate in mice by suppression of NF-κB, ERK, JNK, p38 MAPK, PI3 K and Akt.[65] Intimal hyperplasia is based on vascular inflammation and NF-κB activation and the HAT PCAF promotes NF-κB-regulated inflammation. Garcinol suppressed CCL2 and TNF-α expression in leukocytes and vascular smooth muscle cells and
reduced arterial adherence and infiltration by leukocytes and macrophages in vivo when administered in a Pluronic gel enabling a slow garcinol drug release.\textsuperscript{[66]} In contrast to these and other previous findings about the considerable anti-inflammatory activities of garcinol, a newer study described the enhancement of lipopolysaccharide (LPS)-induced inflammation by intraperitoneally administered garcinol (injection of 10 mg/kg in DMSO) both in vitro and in vivo.\textsuperscript{[6,67]} The expression of TNF-\(\alpha\) and IL-6 was markedly increased by garcinol in this case, which was correlated with reduced acetylation of NF-\(\kappa B\). Hence, more research is necessary into the positive and negative effects of garcinol on various forms of inflammation processes.

Orally administered isogarcinol (100 mg/kg) showed significant activity against collagen-induced arthritis (CIA) and xylene-induced ear edema in mice. Reduced bone and cartilage damage as well as low concentrations of inflammatory cytokines were observed upon isogarcinol treatment of CIA mice. Suppression of the expression of NF-\(\kappa B\), iNOS, COX-2, NFAT and IL-2 was observed after treatment with isogarcinol from in vitro experiments.\textsuperscript{[68]} The same group investigated the activity of isogarcinol against systemic lupus erythematosus (SLE). Mice with chronic graft-versus-host disease (cGVHD, an SLE in vivo model) were treated with isogarcinol (60 mg/kg) leading to reduced renal histopathology and proteinuria as well as normalized serum biochemical indicator.\textsuperscript{[69]} Isogarcinol (100 mg/kg, orally) also amended skin lesions (similar to psoriasis) induced by exposure to imiquimod in mice. Suppression of IL-23/Th17 axis genes of isogarcinol-treated mice was observed while isogarcinol was less toxic to liver and kidneys than cyclosporine A.\textsuperscript{[70]}

A diet of garcinol (5 mg/kg per day) in groundnut oil was given to male Wistar rats in order to investigate any drug effects on peritoneal macrophages of garcinol-fed rats. It showed positive effects and reduced excretion of lysosomal enzymes such as collagenase, elastase and hyaluronidase.\textsuperscript{[71]} In addition, isogarcinol exerted its immune modulatory effects by direct binding and inhibition of calcineurin.\textsuperscript{[72]} Histone acetylation was also correlated with liver inflammation and acute liver failure in mice and treatment with garcinol (20 mg/kg/day, i.p.) suppressed histone acetylation and prolonged survival of mice suffering from acute liver failure.\textsuperscript{[73]} In endometriosis models, garcinol (0.2 \(\mu g/g/day\), i.p.) could replace the function of the transcription factor KLF11, a repressor of scar-tissue collagen (COL1 A1/Col1a1), leading to fibrosis reversal in Klf11\(^{-/-}\) animals.\textsuperscript{[74]} Obesity-related inflammation was regulated by garcinol via increase of levels of intestinal commensal bacteria Akkermansia. Garcinol blocked the formation of high fat diet (HFD)-induced obesity and suppressed glutamate pyruvate transaminase, cholesterol and triacylglycerol in the plasma of animals fed with garcinol.\textsuperscript{[75]} Pretreatment of leptin-stimulated cells with garcinol (1 \(\mu M\)) also inhibited leptin-associated cPLA\(_2\) expression via inhibition of p300 HAT.\textsuperscript{[76]} In addition, garcinol displayed beneficial effects on diabetic Wistar rats and oral application of garcinol (10 mg/kg and 20 mg/kg) normalized diabetic parameters in the rats similar to the antidiabetic drug glibenclamide.\textsuperscript{[77]} Osteolysis is often based on activated osteoclasts which are bone-resorbing osteoimmune cells.\textsuperscript{[78]} Osteoclastogenesis relies on RANKL (receptor activator of NF-\(\kappa B\)) and treatment of BMM cells (bone marrow monocytes) with garcinol in vitro and of C57BL/6 mice in vivo (mouse calvarial osteolysis model. sub-cutaneous injection of 5 mg/kg in) suppressed osteoclastogenesis by downregulation of PI3 K/Akt, MAPK and NF-\(\kappa B\) signaling.\textsuperscript{[79]}

Effects of garcinol and isogarcinol on various neural inflammation and neural degenerative disease models were disclosed. Experimental autoimmune encephalomyelitis (EAE) is a preclinical murine model for the investigation of multiple sclerosis (MS). EAE mice treated with isogarcinol (100 mg/kg/day, orally) showed lower degrees of intracranial lesions and demyelination of the spinal cord due to drug interference with the JAK/STAT signaling pathway.\textsuperscript{[80]} Thus, isogarcinol can be a little toxic alternative to currently applied drugs for the treatment of MS. Intrathecal injections of garcinol in rats (L\(_2\) spinal nerve ligation/SNL model) prolonged thermal withdrawal latency (TWL) and, thus, reduced neuropathic pain likely via suppression of acetyl-p65.\textsuperscript{[81]} Neuroinflammation of microglia was suppressed by treatment with garcinol and downregulation of NF-\(\kappa B\) signaling. Garcinol also reduced the expression of COX-2/PGE2, iNOS and interleukins (IL-1b, IL-6) in the SNL rat spinal cord.\textsuperscript{[82]} Monoamine oxidase-B (MAO–B) metabolizes dopamine and, thus, represents a suitable target for the treatment of Parkinson’s disease (PD) based on dopamine depletion in certain parts of the brain. Garcinol exhibited a distinct MAO–B inhibition similar to known MAO–B inhibitors and together with its neuroprotective effects, this compound appears particularly promising for the treatment of PD.\textsuperscript{[83]} Garcinol also reduced the side-effects of dopamine replacement therapy by L-DOPA. Dyskinesia induced by L-DOPA in 6-hydroxydopamine (6-OHDA)-lesioned mice was reduced by co-treatment with garcinol (5 mg/kg,}
Garcinol also inhibited catechol-O-methyltransferase leading to an increased L-DOPA bioavailability and it reduced hyperhomocysteinemia associated with L-DOPA treatment. This indicates the great potential of garcinol for the treatment of PD in combination with L-DOPA.\cite{83} It was observed that garcinol-pretreatment (50, 100 or 200 mg/kg, i.p.) of mice with pentylenetetrazole (PTZ)-induced epilepsy led to a marked decrease of mortality and of seizure scores. In addition, the memory and cognition of these garcinol-treated mice improved distinctly. Suppression of BDNF and TrkB by garcinol as well as garcinol-induced upregulation of GABA\textsubscript{A} and GAD65 were identified as anti-epileptic modes of action of garcinol.\cite{86} Garcinol (10 mg/kg, i.p.) also showed beneficial effects in rats exposed to cocaine and it inhibited reinstatement by reconsolidation-based modes following cocaine reactivation.\cite{87,88} Reactivated memories were affected by garcinol which displayed long-lasting effects and, thus, garcinol can support drug abstinence and be a suitable therapy for psychopathologies such as drug addiction. Indeed, memory processes in honeybees strongly depend on HAT activity and histone H3 acetylation by treatment with garcinol or C646.\cite{89}

Garcinol isolated from the fruits of the Thai plant *Garcinia dulcis* also showed vasorelaxant activity. It might be a suitable drug for the treatment of hypertension due to its antioxidant activity. Injection of hypertensive 2 K1 C (2-kidneys-1-clip) rats with low doses of garcinol (0.1 mg/kg, i.v.) led to hypotensive effects and reduced arterial blood pressure, heart rate, plasma malondialdehyde values, and eNOS expression.\cite{93}

Eryptosis is a programmed cell death process to eliminate defective erythrocytes (prior to nephrotoxic hemolysis) analogously to apoptosis of damaged cells with nuclei.\cite{94} In particular, eryptosis has been identified as a mechanism to fight infection with *Plasmodium* (malaria), for example, in sickle-cell trait, in order to eliminate infected erythrocytes and the parasites therein. Human erythrocytes treated with garcinol (5 \mu M) underwent eryptosis according to increased annexin-V binding, increased ROS formation and reduced ATP level of the cytosol.\cite{95} Thus, garcinol has the potential to fight *Plasmodium*-caused diseases via this peculiar mode of action.

### 7. Conclusions

The chemistry and biology of garcinol and isogarcinol are active and prospering fields of research. The total synthesis of garcinol by Socolsky and Plietker represents a chemical highlight of the past years and enables the fine-tuning of the garcinol molecule concerning improved biological activities by preparation of synthetic garcinol derivatives. The identification of new HATs as targets of garcinol or isogarcinol broadens the scope of application of these natural products including activities against viral and parasitic models. In addition, their distinct activities against cancer stem-like cells warrant studies against further tumor models. One report has appeared that described a promoting effect on LPS-induced inflammation processes. This is in stark contrast to many other publications which describe garcinol or isogarcinol as potent agents against various inflammation processes. Future studies will show if this is just a solitary case. It is noteworthy that garcinol was also found active against models of various neurological diseases such as EAE, Parkinson disease, epilepsy or drug addiction. These discoveries underline once more the potential of garcinol and isogarcinol as valuable drug candidates.
Author Contribution Statement

Bernhard Biersack carried out the literature search and wrote the manuscript. Rainer Schobert revised and proofread the manuscript.

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