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Review Article

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Recent Findings on *Alpinia Galanga* (L.) Wild for the Treatment of Arthritis Part-2

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ABSTRACT

Arthritic inflammation of joints affects people of all age groups. The treatment is a challenge as arthritis is a complex disease and evolves over years. Patients often have to take medicines for the rest of their life. Commonly prescribed medicines like analgesic, glucocorticoids and non-steroidal anti-inflammatory drugs have side effects. The new disease modifying medicines are costly. People in the healthcare system are assessing the dynamics of complementary and alternative medicines. One such remedy is *Alpinia galanga* (AG) of Zingiberaceae family. It is characterized by the presence of rhizome, wide leaves and terminal inflorescence. The references for its medicinal uses are found in traditional medicines. It is cultivated in tropical regions of south east Asia. Its rhizome is highly aromatic and most frequently used as a food and medicine. The various extracts of AG are prepared by the researchers and studied for its phytoconstituents and pharmacological activities. Clinical, *in vitro*, *in vivo* and *in silico* experimentation techniques are used to validate the claims for various therapeutic activities. This article focuses on reviewing literature to ascertain anti-arthritic potential of AG. The article has been divided in 2 parts and includes analgesic, anti-arthritic, anti-inflammatory, antioxidant, other therapeutic effects as well as safety and toxicity of AG.

Key Words: Greater galangal, Ginger, Antioxidant, Anti-inflammatory, Analgesic, Rheumatic, Rhizome.

INTRODUCTION

The plants of Zingiberaceae family have contributed a lot toward food and medicine. The readers have been introduced to *Alpinia galanga* (AG), plant of Zingiberaceae family, pathophysiology of arthritis as well as analgesic and anti-arthritic effect of AG in part 1 of the article. Other pharmacological effects useful for the treatment of arthritis and safety and toxicity of AG are discussed in this part.

ANTI-INFLAMMATORY EFFECT

Subhash et al.[1] administered ethanolic extract of AG at doses of 100,200 and 400mg/kg per oral. Inflammation was induced inrats by injecting 10% carrageenan solution. The volume of pleural exudates and the number of migrating leukocytes was decreased in rats treated with the extract in a dose dependent manner. The percentage inhibition produced by 400 mg/kg ethanolic extract was almost similar to the standard drug indomethacin.

In a similar study ethanolic extract of AG at dose of 250 mg/kgin male Wistar rats injected with 0.1ml of 1% carrageenan, produced 52.5percentage of inhibition of inflammation at the end of 3 hrs. In comparison to it, indomethacin showed 68.75 percentage of inhibition.[2]

Unnisa et al.[3] prepared alkaloids, glycosides, carbohydrates, tannins, flavonoids and saponins rich methanolic extract of AG. This extract showed significantly higher inhibition of carrageenan induced inflammation in Wistar rats as compared to petroleum, chloroform and aqueous methanolic extracts. With respect to onset and duration of action, methanolic extract at 500mg/kg was comparable to ibuprofen.

Ghosh et al.[4] extracted AG twice with absolute alcohol and this extract was lyophilized. They further studied the extract of AG for anti-inflammatory effect using inflammation inducers like carrageenan, bradykinin and 5-HT in rats. AG extract, phenylbutazone and dexamethasone were administered to separate groups of albino rats at a dose of 50 mg/kg. Inhibition of inflammation due to AG extract was 32.22%, 37.70% and 35.21% respectively. Though inhibition of inflammation was less as compared to standard drugs, it was

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significant as compared to control. They also studied the anti-inflammatory effect in rats on inflammation induction by formaldehyde. On 13th day, inhibition of inflammation due to AG extract, phenylbutazone and dexamethasone was 55.75%, 64.8% and 57.72% respectively.

In yet another study, the total alcoholic (TAE) and aqueous (TAQ) extracts of rhizome of AG were prepared. These extracts were tested in carrageenan induced paw oedema and cotton pellet induced granuloma models for acute and subacute inflammation. The extracts at 100 mg/kg exhibited significant anti-inflammatory activity, comparable to that of phenylbutazone.[5]

Baldo and Serrano prepared juice of fresh rhizomes at 3 concentrations of 25%, 50% and 75%. Colitis was induced in male albino mice by administering 1 ml of 5% Acetic Acid transrectally. The mice were treated with AG juice for seven days. Acetic acid caused intestinal lesions. Histological examination of colon showed that these lesions were healed by treatment of juice. The mice treated with 75% juice showed weight again as there was better healing.[6]

Pothacharoen et al.[7] extracted dried rhizomes of AG with hexane. The dried hexane extract was separated by column chromatography using gradient elution of hexane and ethyl acetate. Elution started with hexane and stopped when ethyl acetate content reached 20%. The four fractions were collected. For each fraction, HPLC profile was studied. Synovial fibroblasts were collected from flat pad syndrome patients. The isolated synovial fibroblast at passage 4 were inflamed with 10 ng/ml human recombinant IL-1β. The different concentrations of individual fractions of hexane extract were added to expression of genes involved in IL-1β induced catabolic activities. AG hexane extract bfraction 4 could suppressIL-1β-induced MMP-2, MMP-1,MMP-3, MMP-13, as well as Cox-2 expression. Though the precise mechanism was not elucidated, an anti-inflammatory effect was confirmed.

Dried rhizomes of AG were extracted with hexane by percolation. Subsequently, the residue was percolated with ethyl acetate, acetone and methanol and extracts were collected. The porcine cartilage explants were stimulated with IL-1β and inhibitory effects of various extracts at different concentrations were studied. Among all extracts, acetone extract had best ability to maintain the levels of s-GAGs, HA and MMP-2. Hence, acetone extract was studied further. The p-hydroxycinnamaldehyde 1 (3- (4-hydroxy-phenyl)-propenal) was isolated from the extract. The isolated phytoconstituent showed similar effect on IL-1β inflamed porcine cartilage explant. It suppressed the release of HA, s-GAGs & MMP-2, reduced expression of the MMP-3 and MMP-13 and induced expression of collagen, SOX9 and aggrecan core protein.[8]

George et al.[9] defatted powdered rhizomes of AG with hexane. This AG residue was subsequently extracted with 70% alcohol. The solvent was evaporated and the residue was collected. Cells of Murine macrophage cell lines (RAW 264.7) were treated with AG extract (6.25 to 200 µg/ml) for 1hr and then with lipopolysaccharides (1 µg/ml) for 24 h. In comparison to untreated cells, cells pretreated with AG extract showed down regulation of pro-inflammatory mediators TNF-α, IL-6, nitric oxide, reactive oxygen species and up regulation of anti-inflammatory mediator IL-10. The levels of inflammatory enzymes like iNOS, COX-2, and MMP-9 were low as compared to untreated cells. AG extract inhibited nuclear translocation of nuclear factor-κB(NFκB) further resulting in inhibition of the TLR4 pathway of inflammation cascade.

In a rodent model of lipopolysaccharide-induced inflammation, constituents of AG, kaempferol and galangin in two separate experiments showed anti-inflammatory activity. Kaempferol markedly reduced expression of cytokines and suppressed phosphorylation of (NFκB).[10,11]

ANTIOXIDANT EFFECT

Morikawa et al.[12] compared inhibitory effects of constituents of AG viz. galanganal, galanganols B and C, trans-p-hydroxycinnamaldehyde, 1′-acetoxychavicol acetate, 1′-acetoxyeugenol acetate, trans-p-coumaryl alcohol, and trans-p-coumaryl diacetate on nitric oxide production in LPS-Activatedmouse peritoneal macrophages. 1′-acetoxychavicol acetate was found to be the most effective.

Juntachote and Berghofer[13] studied superoxide anion scavenging activity, metal chelating activity, and reducing power activity of hydroalcoholic extract of AG at various concentrations. They observed that antioxidant activity was concentration dependent. They also observed that extract was heat stable and showed maximum antioxidant activity at neutral pH compared to acidic pH.

Mahae and Chaiseri[14] observed that compared to water extract and essential oil, 50% ethanolic extract had higher total phenolic content and higher total flavonoid content. Also 50% ethanolic extract had higher antioxidant activity determined using free radical scavenging and oxygen radical absorbance capacity methods. The major constituents in ethanolic extract were 1′-acetoxycavichol acetate and catechin.

Non-polymeric phenolic (NP) fractions and polymeric tannin (PT) fractions were prepared separately from leaves and rhizomes of AG. NP fraction was obtained in a higher quantity in both the cases. Total phenolic content (TPC) using the Folin-Ciocalteu and ascorbic acid equivalent capacity (AEAC) using 2,2-diphenyl-1-picrylhydrazyl (DPPH) were determined. PT fraction of AG rhizomes showed highest TPC and AEAC.[15]

95% ethanol extract of AG was found to contain 0.970 mg/g gallic acid equivalent of total phenolic contents. The antioxidant activities determined by the b-carotene bleaching method was 70.3%.The GC–MS analysis showed that the main compounds of galangal extract were 1,8-cineole, b-bisabolene, b-caryophyllene and b-selinene.[16]

Melanathuru et al.[17] compared antioxidant activity of two species of Alpinia viz *Alpinia calcarata* and *Alpinia galanga*. Antioxidant activity was studied using techniques like DPPH free radical scavenging assay, reducing power assay, nitric oxide radical scavenging assay, phosphomolybdenum reduction assay. In all studies, AG showed higher antioxidant activity than *Alpinia calcarata.*

Nampoothri et al.[18] found that higher antioxidant activity of AG than of *Alpinia calcarata* was due to higher phenolic contents and two of the phenolic compounds identified were gallic and ellagic acids.

Jitoe et al.[19] extracted AG and other gingers at room temperature for 18 days with acetone and estimated antioxidant activity by thiocyanate and thiobarbituric acid methods. It was observed that despite having curcuminoids, known antioxidants, in trace quantities, AG extract had antioxidant activity stronger than α-tocopherol.

Zaeoung et al.[20]investigated antioxidant potential of methanolic extract of AG rhizome. They further analysed the constituents and found trans-3-acetoxy-1,8-cineole, ar-turmerone, ethyl cinnamate, camphor, and geranial (E-citral) as well as a new compound p-coumaryl- 9-methyl ether.

Essential oil of AG rhizome obtained from the northern region of Thailand was prepared by hydro distillation technique using a Clevenger apparatus. The antioxidant activity of it was studied by DPPH and ABTS free radical decolorization assay. Linear correlation was observed between the two methods. The antioxidant activity could be attributed to 1, 8-cineole, 4-allyphenyl acetate, β-bisabolene, β-pinenethe major compounds detected by GC-MS analysis.[21]

Srividya et al.[22] observed that ethanolic extract of AG exhibited potent antioxidant activity when evaluated by DPPH, lipid peroxidation, hydrogen peroxide radical scavenging and ABTS radical scavenging methods. They further carried out *in vivo* activities. Diabetes mellitus was induced in Wistar rats by intraperitoneal injection of 50mg/kg of Streptozocin. The ethanolic extract of AG was fed to rats at a dose of 200mg/kg and 400mg/kg. Positive and negative controls were included in the study. At the end of 21 days levels of antioxidant enzymes in pancreas viz. GSH, SOD, CAT and TBARS were estimated. Compared to untreated control, AG extract restored these levels in dose dependent manner. AG extract at 400mg/kg showed results comparable to 10mg/kg Glibenclamide treated rats.

AG is rich in phenolic compounds that act as reducing agents, singlet oxygen quenchers, hydrogen donors and metal chelators. A murine macrophage cell line RAW264 cells were stimulated with lipopolysaccharide or interferon-gamma for production of nitric oxide (NO). ACA was found to inhibit NF-kappa B activation and suppressed suppressed NO production dose dependently.[23]

AG also can reduce toxic effects of chemical at other places in the body. Methotrexate (MTX) is a disease modifying anti- rheumatoid medicine. It is prescribed to many patients when conventional therapy fails. The long-term use of MTX causes hepatotoxicity. Galangin, a flavonoid of AG had shown hepatoprotective effect against MTX induced hepatotoxicity.[24] Thus AG can be used alone or in combination with other synthetic or natural medicines.

ANTIANGIOGENIC EFFECT

In human umbilical vascular endothelial cells, ACA suppressed vascular endothelial growth factor (VEGF). In a dose-dependent manner, there was a reduction in proliferation, migration, adhesion and tubulogenesis. Inhibition of microvessel sprouting from aortic rings and suppression of new vasculature formation in Matrigel plugs was observed due to ACA.[25]

ANTIPROLIFERATIVE AND APOPTOTIC EFFECT

The loss of balance between cell proliferation and apoptosis is observed in arthritic joints. The insufficient apoptosis of inflammatory cells leads to disease progression.[26]

Baradwaj et al.[27] extracted ACA from AG by sequential extraction using hexane and methanol with 0.38% yield. They studied antiproliferative activity of ACA against Dukes' type B, colorectal adenocarcinoma (SW480).At an IC50 of 80mM (48 h), ACA suppressed the proliferation of SW480 cells by halting the cell cycle at the G0/G1 checkpoint. ACA was not cytotoxicity towards normal Human Mammary Epithelial Cells (HMEC) but showed apoptotic effect in cancer cells. Cancer chemotherapeutics can be used in the treatment of rheumatoid arthritis as disease modifying drugs.[28,29]

1'S-1'-Acetoxychavicol Acetate has shown apoptotic effect on human cancer cells like breast adenocarcinoma (MCF-7), hepatocyte carcinoma (HepG2), oral squamous carcinoma (HSC-2 and HSC-4), epidermoid cervical carcinoma (CaSki). In MTT cell viability assays IC50 values observed at the end of 24 hrs were MCF-7 (30.0μM), HSC-2 (5.0μM), HSC-4 (5.5 μM), HepG2(18.0 μM), CaSki (17.0 μM).[30] 4'-hydroxycinnamaldehyde extracted from AG showed apoptotic effect in human leukemic HL-60 and U937 cells. The

effect was mediated through a combination of mitochondrial and endoplasmic reticulum stress pathways.[31]When Jurkat cells (human T-cell leukemia cell line) were incubated with galanal A or B for 6 h, DNA fragmentation was observed.[32]

Colonic aberrant crypt foci were induced in male F344 rats by injecting azoxymethane. 100 ppm and 200 ppm of 1'-acetoxychavicol acetate (ACA) isolated from AG was administered through diet. It exhibited xanthine oxidase inhibition and had antiproliferative action.[33] Elevated levels of xanthine oxidase are found in RA.[34] Thus, 1'-acetoxychavicol acetate can be used for the treatment of arthritis. Apart from AC other xanthine oxidase inhibitors were also isolated from AG.[35]

MISCELLANEOUS

AG oil was found to exert anesthetic effect in *Cyprinus carpio* (koi carp)[36] and *Oreochromis niloticus* (Nile tilapia) fish models.[37] The suitable dose of AG oil to induce desired anesthesia were 500 and 700 mg/L respectively.

AG has been found to be effective against *Mycobacterium tuberculosis* through *M. tuberculosis* shikimate kinase (MtSK) inhibitory assays.[38] Since some *Mycobacterium* species are known to cause arthritis, it will be beneficial to explore use of AG in septic arthritis.[39,40]

As rheumatoid arthritis is an autoimmune disease, use of medicaments with immunomodulatory activity helps in arresting the disease progression. In patent US6566405 a novel composition of AG with immunomodulatory action is disclosed. It contains synergistic mixture of aromatic and terpenoid compounds of AG and is useful for autoimmune disorders like arthritis.[41]

SAFETY AND TOXICITY

Ethanolic extract of AG in an acute toxicity study at a dose of 3g/kg in Swiss albino mice showed no signs of toxicity and mortality. Chronic toxicity study was carried out at a dose of 100 mg/kg/day for a period of 3 months. Only 15% lethality was observed.[42] In yet another acute toxicity study, LD50 was estimated to be more than 5g/kg.[43]

Singh et al.[44] carried-out toxicity study in female Albino mice. Ethanolic extracts of AG were administered by gastric intubation. If no mortality was observed, higher dose was administered. No mortality or sign of toxicity was observed at the oral dose of 2000 mg/kg in mice and thus, ethanolic extract was considered nontoxic according to OECD-423 guidelines.

AG is included in a list of Generally Recognized as Safe (GRAS) for food additives by US FDA as galanga root (GRAS 2498), galanga root oleoresin (GRAS 2499) and galanga root oil (GRAS2500).

DISCUSSION

Carrageenan-induced rat paw oedema is a widely used test to determine acute anti-inflammatory activity.[45] Number of phytoconstituents as well as synthetic compounds have been evaluated by this animal model. Carrageenan is found to increase peripheral nitric oxide and number of phytoconstituents of AG have been found to reduce nitric oxide synthesis.[46] Pathophysiology of arthritic joints have indicated that antioxidants can arrest deterioration of joints, if they are made available at thesite.[47] Different conventional and novel dosage forms for various extracts and isolated compounds of AG have been developed for various ailments e.g., tablets, emulgel, silver nanoparticles etc.[48,49] Further research on use of novel drug delivery systems for AG could help in targeted delivery. Antiangiogenic effect, antiproliferative and other effects of AG needs to be studied in detail with focus on effect in arthritic environment.

CONCLUSION

With plethora of activities discussed in part -1 and part-2, we can definitely say use of AG is beneficial to arthritic patient. Validated analytical techniques should be used for ensuring quality of the products. Multi-centre clinical trials in large number of patients are required to decide the dose and dosage regime. Though AG is widely grown in many parts of the world, research in micropropagation techniques could be useful to meet the requirements of demand and supply.[50,51]

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CONFLICTS OF INTEREST

Authors declare no conflict of interest. The authors alone are responsible for the content and writing of this article.

AUTHORS' CONTRIBUTION

Roopam Raut collected and analyzed the data and drafted the manuscript. Jessy Shaji critically reviewed the manuscript. All authors have read and approved the final manuscript.

ETHICAL CLEARANCE

None.

REFERENCES

1. Subash KR, Manjunath K, Rao U. Anti-inflammatory activity of ethanolic extract of *Alpinia galanga* in carrageenan induced pleurisy rats. Natl J Physiol Pharm Pharmacol. 2016Jul 13;6(5): 468-70.
2. Kameswari VL, Sankar VR, Kondaveti SS. Anti-Inflammatory activity of *Alpinia Galanga* in Experimental Animals. J Evid Based Med Healthc. 2015 Mar 02;2(13):1876-79.
3. Unnisa A, Parveen TD. Anti-inflammatory and acute toxicity studies of the extracts from the rhizomes of *Alpiniagalanga* Willd. Der Pharmacia Sinica. 2011Mar;2(2):361-67.
4. Ghosh AK, Banerjee M, Bhattacharyya NK. Anti-inflammatory activity of root of *Alpinia galanga* Willd. Chron Young Sci. 2011 Sep;2(3):139-43.
5. Satish R, Dhananjayan R. Evaluation of anti-inflammatory potential of the rhizome of *Alpinia galanga* linn. Biomed. 2003 Jan;23:91–96.
6. Baldo DE, Serrano JE, Diomerl C, Baldo E. Screening for intestinal anti-inflammatory activity of *Alpinia galanga* against acetic acid-induced colitis in mice (Mus musculus). J Med Plant Res. 2016 Jan;4(1):72-77.
7. Pothacharoen P, Choocheep K, Phitak T, Pompimon W, Kongtawelert P. *Alpinia galanga* extracts downregulate interleukin-1β-induced matrix metalloproteinases expression in human synovial fibroblasts. In Vitro Cell Dev Biol Anim. 2011 Mar;47(3):183-87.
8. Phitak T, Choocheep K, Pothacharoen P, Pompimon W, Premanode B, Kongtawelert P. The effects of p-hydroxycinnamaldehyde from *Alpinia galanga* extracts on human chondrocytes. Phytochem. 2009 Jan;70(2):237-43.
9. George G, Shyni GL, Abraham B, Nisha P, Raghu KG. Downregulation of TLR4/MyD88/p38MAPK and JAK/STAT pathway in RAW 264.7 cells by *Alpinia galanga* reveals its beneficial effects in inflammation. J Ethnopharmacol. 2021 Jul 15;275:114132.
10. Cao R, Fu K, Lv X, Li W, Zhang N. Protective effects of kaempferol on lipopolysaccharide-induced mastitis in mice. Inflammation. 2014 Oct;37(5):1453-58.
11. Shu YS, Tao W, Miao QB, Lu SC, Zhu YB. Galangin dampens mice lipopolysaccharide-induced acute lung injury. Inflammation. 2014 Oct;37(5):1661-68.
12. Morikawa T, Ando S, Matsuda H, Kataoka S, Muraoka O, Yoshikawa M. Inhibitors of nitric oxide production from the rhizomes of *Alpinia galanga*: structures of new 8–9′ linked neolignans and sesquineolignan. Chemand Pharm Bull. 2005 Jun;53(6):625-30.
13. Juntachote T, Berghofer EJ. Antioxidative properties and stability of ethanolic extracts of Holy basil and Galangal. Food chem. 2005 Sep 01;92(2):193-202.
14. Mahae N, Chaiseri S. Antioxidant activities and antioxidative components in extracts of *Alpinia galanga* (L.) Sw. Agric Nat Resour. 2009 Jun 30;43(2):358-69.
15. Chan EW, Ng VP, Tan VV, Low YY. Antioxidant and antibacterial properties of *Alpinia galanga*, *Curcuma longa*, and *Etlingera elatior* (Zingiberaceae). Pharmacogn J. 2011Jun 1;3(22):54-61.
16. Mayachiew P, Devahastin S. Antimicrobial and antioxidant activities of Indian gooseberry and galangal extracts. LWT-Food Sci Technol. 2008 Sep 1;41(7):1153-59.
17. Melanathuru VI, Rengarajan SU, Thangavel NI. Comparative study of antioxidant and anticancer activity of *Alpinia calcarata* and *Alpinia galanga*. Int J Pharm Pharm Sci. 2017 Dec;9:186-93.
18. Nampoothiri SV, Esakkidurai T, Pitchumani K. Identification and quantification of phenolic compounds in *Alpinia galanga* and *Alpinia calcarata* and its relation to free radical quenching properties: a comparative study. J Herbs Spices Med Plants 2015 Apr;21(2):140-47.
19. Jitoe A, Masuda T, Tengah IG, Suprapta DN, Gara IW, Nakatani N. Antioxidant activity of tropical ginger extracts and analysis of the contained curcuminoids. J Agric Food Chem. 1992 Aug;40(8):1337-40.
20. Zaeoung S, Plubrukarn A, Keawpradub N. Cytotoxic and free radical scavenging activities of Zingiberaceous rhizomes. Songklanakarin J Sci Technol. 2005;27(4):799-812.
21. Tachakittirungrod S, Chowwanapoonpohn S. Comparison of antioxidant and antimicrobial activities of essential oils from *Hyptis suaveolens* and *Alpinia galanga* growing in Northern Thailand. CMU J Nat Sci. 2007 Jan;6(1):31-41.
22. Srividya AR, Dhanabal SP, Satish Kumar MN, Parth Kumar HB. Antioxidant and antidiabetic activity of *Alpinia galanga*. Int J Pharmacogn Phytochem Res. 2011 Mar;3(1):6-12.
23. Ohata T, Fukuda K, Murakami A, Ohigashi H, Sugimura T, Wakabayashi K. Inhibition by 1'-acetoxychavicol acetate of lipopolysaccharide-and interferon-gamma-induced nitric oxide production through suppression of inducible nitric oxide synthase gene expression in RAW264 cells. Carcinogenesis. 1998 Jun 1;19(6):1007-12.
24. Alfwuaires MA. Galangin mitigates oxidative stress, inflammation, and apoptosis in a rat model of methotrexate hepatotoxicity. Environ Sci Pollut Res Int. 2022;29(14):20279-20288.
25. Pang X, Zhang L, Lai L, Chen J, Wu Y, Yi Z, et al. 1′-Acetoxychavicol acetate suppresses angiogenesis-mediated human prostate tumor growth by targeting VEGF-mediated Src-FAK-Rho GTPase-signaling pathway. Carcinogenesis. 2011 Jun 1;32(6):904-12.
26. Pope RM. Apoptosis as a therapeutic tool in rheumatoid arthritis. Nature Reviews Immunology. 2002 Jul;2(7):527-35.
27. Baradwaj RG, Rao MV, Kumar TS. Novel purification of 1'S-1'-Acetoxychavicol acetate from *Alpinia galanga* and its cytotoxic plus antiproliferative activity in colorectal adenocarcinoma cell line SW480. Biomed Pharmacother. 2017 Jul 1;91:485-93.
28. Jayashree S, Nirekshana K, Guha G, Bhakta-Guha D. Cancer chemotherapeutics in rheumatoid arthritis: A convoluted connection. Biomed Pharmacother. 2018 Jun 1;102:894-911.
29. Padjen I, Crnogaj MR, Anić B. Conventional disease-modifying agents in rheumatoid arthritis–a review of their current use and role in treatment algorithms. Reumatologia. 2020 Nov 1;58(6):390-400.
30. Awang K, Azmi MN, Aun LI, Aziz AN, Ibrahim H, Nagoor NH. The apoptotic effect of 1's-1'-acetoxychavicol acetate from *Alpinia conchigera* on human cancer cells. Molecules. 2010 Nov 9;15(11):8048-59.
31. Banjerdpongchai R, Punyati P, Nakrob A, Pompimon W, Kongtawelert P. 4′-Hydroxycinnamaldehyde from *Alpinia galanga* (Linn.) induces human leukemic cell apoptosis via mitochondrial and endoplasmic reticulum stress pathways. Asian Pac J Cancer Prev. 2011 Jan 1;12(3):593-98.
32. Miyoshi N, Nakamura Y, Ueda Y, Abe M, Ozawa Y, Uchida K, et al. Dietary ginger constituents, galanals A and B, are potent apoptosis inducers in Human T lymphoma Jurkat cells. Cancer Lett. 2003 Sep 25;199(2):113-19.
33. Tanaka T, Makita H, Kawamori T, Kawabata K, Mori H, Murakami A, et al. A xanthine oxidase inhibitor 1'acetoxychavicol

acetate inhibits azoxymethane-induce colonic aberrant crypt foci in rats. Carcinogenesis. 1997 May 1;18(5):1113-18.
34. Hanachi N, Charef N, Baghiani A, Khennouf S, Derradji Y, Boumerfeg S, et al. Comparison of xanthine oxidase levels in synovial fluid from patients with rheumatoid arthritis and other joint inflammations. Saudi Med J. 2009 Nov 1;30(11):1422-25.
35. Noro T, Sekiya T, Katoh M, Oda Y, Miyase T, Kuroyanagi M, et al. Inhibitors of xanthine oxidase from *Alpinia galanga*. Chem Pharm Bull. 1988 Jan 25;36(1):244-48.
36. Khumpirapang N, Pikulkaew S, Anuchapreeda S, Okonogi S. *Alpinia galanga* oil—A new natural source of fish anaesthetic. Aquac. Res. 2018 Apr;49(4):1546-56.
37. Pikulkaew S, Khumpirapang N, Chaisri W, Okonogi S. Effects of *Alpinia galanga* oil on anesthesia and stress reduction in Oreochromis niloticus. Drug Discov Ther. 2017 Aug 31;11(4):186-92.
38. Patrick M, Zhang Y, Calderón AI. Combination of HRLC–MS with MPP and GNPS data analysis to identify major constituents of *Mt*SK inhibitory *Alpinia galanga* extract. Nat Prod Resh. 2021 Apr 22:1-5.
39. Shu CC, Wang JY, Yu CJ, Lee LN. Mycobacterial arthritis of large joints. Ann Rheum Dis. 2009 Sep 1;68(9):1504-05.
40. Bo M, Jasemi S, Uras G, Erre GL, Passiu G, Sechi LA. Role of infections in the pathogenesis of rheumatoid arthritis: focus on mycobacteria. Microorganisms. 2020 Sep 23;8(10):1459.
41. Weidner MS, Petersen MJ, Jensen NW, inventors; Eurovita AS, assignee. Synergistic compositions containing aromatic compounds and terpenoids present in *alpinia galanga*. United States patent US 6,566,405. 2003 May 20.
42. Qureshi S, Shah AH, Ageel AM. Toxicity studies on *Alpinia galanga* and *Curcuma longa*. Planta medica. 1992 Apr;58(02):124-27.
43. Unnisa A, Parveen TD. Anti-inflammatory and acute toxicity studies of the extracts from the rhizomes of *Alpinia galanga* Willd. Der Pharmacia Sinica. 2011 Mar;2(2):361-67.
44. Hanish Singh JC, Alagarsamy V, Diwan PV, Sathesh Kumar S, Nisha JC, Narsimha Reddy Y. Neuroprotective effect of *Alpinia galanga* (L.) fractions on Aβ (25–35) induced amnesia in mice. J Ethnopharmacol. 2011 Oct 31;138(1):85-91.
45. Necas J, Bartosikova L. Carrageenan: a review. Veterinarni medicina. 2013 Jun 1;58(6).
46. Omote K, Hazama K, Kawamata T, Kawamata M, Nakayaka Y, Toriyabe M, et al. Peripheral nitric oxide in carrageenan-induced inflammation. Brain research. 2001 Sep 7;912(2):171-5.
47. Arulselvan P, Fard MT, Tan WS, Gothai S, Fakurazi S, Norhaizan ME, et al. Role of antioxidants and natural products in inflammation. Oxid Med Cell Longev. 2016 Oct 10:5276130.
48. Putranti W, Dewi NA, Widiyastuti L. Standardization of extract and characterization of emulgel formula of lengkuas(*Alpinia galanga* (L.) Willd) rhizome extract. Jurnal Farmasi Sains dan Komunitas. 2018 Nov;15(2):81-91.
49. Joseph S, Mathew B. Microwave assisted biosynthesis of silver nanoparticles using the rhizome extract of *Alpinia galanga* and evaluation of their catalytic and antimicrobial activities. J Nanopart. 2014;2014:967802.
50. Singh NM, Chanu LA, Devi YP, Singh WR, Singh HB. Micropropagation-an in vitro technique for the conservation of *Alpinia galanga*. Adv Appl Sci Res. 2014;5(3):259-63.
51. Borthakur MI, Hazarika J, Singh RS. A protocol for micropropagation of *Alpinia galanga*. Plant Cell Tissue Organ Cult. 1998 Dec;55(3):231-33.