ANACARDIC

Anacardic acid (anacardic) is a bioactive phytochemical found in the cashew nut shell of *Anacardium occidentale* (the cashew tree). Chemically, Anacardic is a mixture of several closely related organic compounds, each consisting of salicylic acid substituted with an alkyl chain (Hemshekhar, Santhosh, Kemparaju and Girish, 2011) Anacardic has a long history as a natural treatment. Leaves or nut shell extracts from Anacardium occidentale have long been used to treat inflammation and other conditions, including asthma, ulcers, and cancer (Hollands, Corriden, Gysler, Dahesh, Olson, Raza Ali, Kunkel, Lin, Forli, Newton, Kumar, Nair, Perry, Nizet, 2016). Anacardic and its derivatives are well-known for their therapeutic applications ranging from antitumor, antibacterial, antioxidant, anticancer, anti-inflammatory, and gastroprotective properties. Recent studies show that Anacardic derivatives exert their action in treating ovarian cancer, prostate cancer, breast carcinoma, and lung carcinoma through various mechanisms. (Zafa, Gupta, Thangavel, Khatana, Sani, Ghosal, Tandon, & Nishat, 2020).

Antianxiety activity

Mouse experiments showed Anacardic has powerful anxiolytic (antianxiety) effects without myorelaxant and sedative effects, nor did it cause a decrease in locomotor activity. The effects were due to Anacardic's antioxidant and lipid peroxidation inhibitory activity. Anacardic exhibited GABAA receptor mediated anxiolytic activity with the lack of myorelaxation and genotoxicity (Gomes Júnior, Tchekalarova, Machado, Moura, Paz, da Mata, Nogueira, Islam, Rios, Graças Lopes Citó, Uddin, Shilpi, Das, Lopes, and Melo-Cavalcante (2018).

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Antibacterial properties

Anacardic has been shown to exhibit direct antimicrobial activity against a number of bacterial species, including Propionibacterium acnes, Staphylococcus aureus, and Helicobacter pylori (Hollands, Corriden, Gysler, Dahesh, Olson, Raza Ali, Kunkel, Lin, Forli, Newton, Kumar, Nair, Perry, Nizet, 2016).

Researchers found that anacardic stimulates the production of reactive oxygen species and neutrophil extracellular traps, two mechanisms utilized by neutrophils to kill invading bacteria. Molecular modeling and pharmacological inhibitor studies suggest anacardic stimulation of neutrophils occurs in a PI3K-dependent manner through activation of surface-expressed G protein-coupled sphingosine-1-phosphate receptors. Neutrophil extracellular traps produced in response to anacardic are bactericidal and complement select direct antimicrobial activities of the compound (Hollands, Corriden, Gysler, Dahesh, Olson, Raza Ali, Kunkel, Lin, Forli, Newton, Kumar, Nair, Perry, Nizet, 2016).

Anti-cancer activity

Anacardic with varied chain length induced cytotoxicity towards several human cancer cell lines in vitro. The anti-cancer activity exhibited by Anacardic could be due to their ability to act as surfactants. Anacardic displayed effective inhibition towards the proliferation of ERα-expressing breast cancer cells.

Anacardic has been shown to exert anti-proliferative activity in cancer cells such as breast, lung, prostate and pancreatic cells (Park, Upton, Blackmon, Dixon, Craver, Neal, & Perkins, 2018).

Kim, Shin. Kim, Kim, Lee, Lee, and Chung investigated the impact of Anacardic on UV exposure of the skin. UV exposure of the skin induces proinflammatory

cytokines such as interleukin-6 (IL-6), mediated by nuclear factor kappa B (NF-κB) activation, which affects the expression levels of multiple target genes, such as matrix metalloproteinases (MMPs) and type I procollagen, leading to the appearance of wrinkles in photoaged skin, as well as to acute inflammatory responses. They found that Anacardic reduced ultraviolet irradiation-induced damage to human skin. The authors report that Anacardic suppression of p300 HAT using p300 inhibited the UV-induced MMP-1 gene transcription and histone modification in human dermal fibroblasts in vitro. Additionally, Anacardic could suppress the UV-induced histone modification, as well as MMP-13, MMP-9, cyclooxygenase-2, and tumor necrosis factor-α expression in hairless mouse skin in vivo. Adding to the literature, the authors noted Anacardic inhibits the HAT activities of transcription coactivators, p300 and p300/cyclic AMP response element-binding protein-associated factor (pCAF) and suppresses the NF-κB-regulated pathway, reducing the level of IL-6 and tyrosinase activity, and exerting anti-inflammatory and anticancer effects.

Anacardic induces cell apoptosis of prostatic cancer through autophagy by ER stress/DAPK3/Akt signaling pathway. Tan, Jiang, Yin, He, Liu, Long and Yao (2017) found that anacardic inhibited cell proliferation, induced apoptosis and caspase-3/9 activities and Bax protein expression of prostatic cancer. Anacardic induced the ER stress inducing factors (BiP, CHOP, p-eIF2α), autophagy, LC3, Beclin-1, Atg 7 and DAPK3 protein expression, and suppressed p-Akt and p-mTOR protein expression of prostatic cancer.

Zhao, Zhang, Cai, Zhang, Kong, Ge, Du, Liang, & Dong (2018) studied the Anticancer effects of plant derived Anacardic on human breast cancer MDA-MB-231 cells. Anacardic, which is commonly seen in natural plants of Anacardiaceae, exhibits potent Hsp90 ATPase inhibition activity. The authors found that Anacardic inhibited cell proliferation, induced G0/G1-phase cell cycle arrest, suppressed cell invasion and migration, and induced apoptosis in the MDA-MB-231 cells.

Antidepressant activity

Júnior, Tchekalarova, da Conceição Machado, et al (2019) an antidepressant-like effect of anacardic in mice via the L-arginine–nitric oxide–serotonergic system. Results suggest that Anacardic exerts antidepressant-like activity, especially at higher doses, possibly by inhibiting serotonin and 5HT-1A reuptake receptors and by inhibiting NO synthetase and guanylyl cyclase enzymes. Additionally, Anacardic exhibited antioxidant effects in S. cerevisiae. This antioxidant capacity may be linked to its antidepressant-like effect but does not interact with α- and β-adrenoceptor receptors. In conclusion, Anacardic may be used as a promising agent to treat depression, especially which arises from oxidative stress.

Antidiabetic activity

Activation of adenosine monophosphate-activated protein kinase by Anacardic likely increases plasma membrane glucose transporters, resulting in elevated glucose uptake. In addition, the dysfunction of mitochondrial oxidative phosphorylation may enhance glycolysis and contribute to increased glucose uptake (Tedong, Madiraju, Martineau, Vallerand. Arnason, Desire, Lavoie, Kamtchouing and Haddad, 2010).

Antifungal activity

Plasma membrane constriction, chromatin condensation, DNA degradation, and externalization of phosphatidylserine (PS) indicated that anacardic induces apoptotic cell death in the single celled fungus, S. cerevisiae. Interestingly, instead of the increase in the intracellular reactive oxygen species (ROS) normally observed during apoptosis, anacardic caused a decrease in the intracellular ROS levels (Muzaffa & Chattoo, 2016).

Anti-inflammatory

Anacardic blocked NF-κB by inhibiting IKK and not by directly interfering with DNA binding, which led to the suppression of phosphorylation and the degradation of IkB. Recent studies indicated that TAK1 plays a major role in the canonical pathway activated by cytokines through its interaction with TAB 1 and TAB 2.

Yang, Zhang, Wang, Meng, & Wang (2018) examined the therapeutic potential of anacardic in treating rheumatoid arthritis (RA). They explored the effects of anacardic on collagen-induced arthritis (CIA) in mice and on the proliferation and invasion of RA fibroblast-like synoviocytes (RA-FLSs). The serum levels of tumor necrosis factor alpha (TNF- α) and interleutkin-1beta (IL- 1β) were significantly lowered by anacardic. In vitro assays demonstrated that anacardic impaired the proliferation and invasion abilities of RA-FLSs in the presence of TNF- α or IL- 1β. In conclusion, anacardic may serve as a promising agent in the treatment of rheumatoid arthritis.

Júnior, Islam, Nicolau, de Souza, Araújo, de Oliveira, Nogueira, Lopes, Medeiros, Mubarak Melo-Cavalcante (2020) established that Anacardic exhibits anti-inflammatory and antinociceptive actions and also reduces oxidative stress in acute experimental models. Results from their study revealed that Anacardic inhibits edema, leukocyte and neutrophil migration to the intraperitoneal cavity, diminished myeloperoxidase activity and malondialdehyde concentration, and increased the levels of reduced glutathione. In nociceptive tests, it reduced pain via interaction with opioid receptors.

Disruption of the finely tuned osteoblast–osteoclast balance is the underlying basis of several inflammatory bone diseases, such as osteomyelitis, osteoporosis, and septic arthritis. Prolonged and unrestrained exposure to an inflammatory environment results in reduction of bone mineral density by downregulating

osteoblast differentiation. Anacardic has been shown in the laboratory to have an inhibitory effect on gelatinases (MMP2 and MMP9) which are over-expressed in numerous inflammatory conditions. Venugopal, Nambiar, & Nair (2021) study demonstrated that Anacardic promotes osteoblast differentiation in lipopolysaccharide-treated osteosarcoma cells (MG63) by upregulating specific markers, like osteocalcin, receptor activator of NF-κB ligand, and alkaline phosphatase. Furthermore, expression of the negative regulators, such as nuclear factor-κB, matrix metalloproteinases (MMPs), namely MMP13, and MMP1, along with several inflammatory markers, such as Interleukin-1β and Nod-like receptor protein 3 were downregulated by Anacardic. This suggests that Anacardic may be a useful tool in the management of inflammatory bone diseases.

The incidence of gastric mucosa lesions in the adult population has increased mainly due to the continued use of nonsteroidal anti-inflammatory drugs (NSAIDs). da Silva, Braga, de Oliveira, Tinti, de Carvalho, Lazarini & Ruiz (2021) study demonstrated that the carotenoid and anacardic enriched extract obtained from cashew apple pomace is a promising raw material for the development of herbal medicine and/or functional food supplements for the adjuvant treatment of NSAIDs-induced gastric ulcers.

Antioxidant activity

Anacardic effectively prevents cell damage induced by hydrogen peroxide because this can be converted to ROS, hydroxyl radicals, in the presence of metal ions. Anacardic acts as an antioxidant in multiple ways including inhibition of various pro-oxidant enzymes involved in the production of ROS and by chelating the divalent metal ions. The high selectivity of Anacardic towards Fe2+ and Cu2+ ions could be a considerable advantage as an antioxidant. Anacardic could play an important role in reducing oxidative stress-induced physiological damage, neurodegenerative disorders, including cognitive deficits that occur during normal

cerebral ageing and in the treatment of Alzheimer's and Parkinson's diseases. (Hollands, Corriden, Gysler, Dahesh, Olson, Raza Ali, Kunkel, Lin, Forli, Newton, Kumar, Nair, Perry, Nizet, 2016).

Antiparasitic activity

Echinococcosis is a zoonotic infection caused by cestode species of the genus Echinococcus. Anacardic presented a high activity against metacestodes of Echinococcus multilocularis (E. multilocularis) and Echinococcus granulosus sensu stricto (E. granulosus s.s.) in vitro and in vivo. The study found that Anacardic showed promise as a potential candidate drug for echinococcosis treatment (Yuan, Song, Lv, Xin, Wang, Gao, Zhang, Liao, Lian & Jing (2019).

Antiviral properties

Anacardic is a specific covalent inhibitor of SARS-CoV-2 cysteine proteases and was shown to inhibit SARS-CoV-2 replication in vitro at nontoxic concentrations (Chen, Cui, Cooper, Zhang, Lee, Chen, Wang, Liu, Rong, Du 2021).

Cardiovascular protection

Cardiac hypertrophy (the enlargement of an organ or tissue from the increase in size of its cells) is a complex process induced by the activation of multiple signaling pathways. Anacardic, a histone acetyltransferase (HAT) inhibitor, attenuates phenylephrine (PE)-induced cardiac hypertrophy by downregulating histone H3 acetylation at lysine 9 (H3K9ac). In looking to understand the mechanism involved, researchers demonstrated that Anacardic attenuated the overexpression of cardiac hypertrophy-related genes (MEF2A, ANP, BNP, and β-MHC), preventing cardiomyocyte hypertrophy and dysfunction. These results revealed a novel mechanism through which Ananacardic might protect against PE-induced

cardiomyocyte hypertrophy. Specifically, Anacardic inhibits the effects of JNK signaling on HATs-mediated histone acetylation, and could therefore be used to prevent and treat pathological cardiac hypertrophy Peng, Peng, Luo, Wu, Mao, Zhang, & Han (2021).

Trevisan, Ricarte, Dos Santos, Almeida, Ulrich & Owen (2018) looked at the potential of Anacardic in reducing hypertension. Angiotensin-I-converting enzyme inhibitors (ACEi) have been shown to be very efficient in the prevention of hypertension. ACEi are also implicated (by their ability to reduce the product of ACE activity namely angiotensin-II levels. The capacity of anacardic to inhibit ACE thereby represents the most potent naturally available plant chemicals described so far, as a potential means of reducing hypertension. Additionally, the inhibition of angiotensin II production indicated that anacardic could also have utility in cancer prevention and recurrence, and reduction of cardiotoxicity during chemotherapy.

HAT inhibitory activity

Histone acetyltransferases (HATs) are a group of enzymes that play a significant role in the regulation of gene expression. These are covalently modifying the N-terminal lysine residues of histones by the addition of acetyl groups from acetyl-CoA. Dysfunction of these enzymes is often associated with the manifestation of numerous pathophysiological disorders, predominantly cancer, inflammatory and neurological diseases.

Anacardic was found to be a compelling non-competitive inhibitor of p300 and p300/CBP-associated factor (PACF) HATs activities. Even though Anacardic does not affect DNA transcription directly, HAT-dependent transcription from a chromatin template was strongly inhibited.

Immune function

Anacardic modulates reactive oxygen species (ROS), is an inhibitor of eukaryotic histone acetyltransferase, that has been shown to inhibit NFκB activities and, more recently, matrix metalloproteinase activity (Hollands, Corriden, Gysler, Dahesh, Olson, Raza Ali, Kunkel, Lin, Forli, Newton, Kumar, Nair, Perry, Nizet, 2016).

Metabolic Activity

Adipogenesis is the process by which fat-laden cells, that is, adipocytes, develop and accumulate as adipose tissue at various sites in the body, both as subcutaneous fat and as depots. Anacardic inhibits lipid accumulation during adipogenesis in 3T3-L1 preadipocytes and suppresses mRNA expressions of the genes implicated in lipogenesis and their transcription factors. These findings indicate that Anacardic acts as a Hsp90/Akt signaling inhibitor, and may be a possible anti-adipogenic agent (Lee, Chung, Chung, & Choi, 2021).

Anacardic alleviates metabolic dysfunction. Anacardic has been shown to increase glucose uptake by upregulating plasma membrane glucose transporters in vitro (Chung, Ju Shin, Choi, Ho Park, and Hwang (2020).

The effects of anacardic on metabolic disorders related to obesity, fatty liver disease, and diabetes were evaluated using both in vitro and in vivo models. The application of Anacardic led to a reduction in lipid accumulation in 3T3-L1 cells without observable cytotoxicity in studies on mice (Chung, Ju Shin, Choi, Ho Park, and Hwang (2020).

It is important to control lipid levels to manage metabolic diseases, as high lipid levels in the body cause chronic diseases. Because lipids are susceptible to oxidation, high levels of free fatty acids in the plasma and large amounts of fat stored in adipose tissues can induce oxidative stress. Inflammation from this stress

can then lead to obesity. Adipose tissue dysfunction caused by hypertrophied adipocytes stimulates the secretion of proinflammatory adipokines such as leptin, resistin, visfatin, and tumor necrosis factor (TNF)-α. In turn, the overproduction of adipokines promotes obesity-associated metabolic diseases, including diabetes and cardiovascular disease. Adipokines are associated with inflammation that is linked to metabolic diseases, although the specific mechanisms remain unknown. Nevertheless, PPAR-γ and FAS have been identified as biomarkers for evaluating adipocyte differentiation and are associated with adipokine productions. When levels of PPAR-γ, a lipid-activated transcription factor, increase in adipose tissue, fatty acids bind to receptors and are converted to triglycerides. This process activates a target gene that induces the conversion of preadipocytes to mature adipocytes. FAS is a key lipogenic enzyme that catalyzes the synthesis of long-chain fatty acids, that is, converting acetyl-CoA and malonyl-CoA to palmitate, which are then stored in adipose tissue. Research revealed that Anacardic inhibited lipid accumulation and decreased PPAR-γ and FAS expression levels, which were initially increased during MDI-induced adipocyte differentiation. Therefore, Anacardic may inhibit fat accumulation by suppressing the production of PPAR-γ and FAS-mediated cytokines. The antioxidant properties of Anacardic may also help prevent adipocyte-induced oxidative stress and adipokine production (Chung, Ju Shin, Choi, Ho Park, and Hwang (2020).

Neuroprotective Activity

Researchers found that oral administration of anacardic prevented behavioral changes and oxidative stress induced by the pesticide Rotenone in a rat model of parkinson's disease. Anacardic has a modulatory action on the mitochondria and SOD gene expression. These data suggest that Anacardic have promising neuroprotective action against degenerative changes in Parkinson's disease (Medeiros-Linard, Andrade-da-Costa, Augusto, Sereniki, Trevisan, Perreira, de Souza, Braz, Lagranha, de Souza, Wanderley, Smailli & Lafayette, 2018).

Mughairbi, Nawaz, Khan, Hassan, Mahmood, Ahmed, Alshamali, Ahmed, and Bashir (2021) investigated the neuroprotective effects of Anacardic against glutamate induced cell death in the adrenal pheochromocytoma cell line of rats (PC12 cells). These findings suggest that the traditional use of Anacardic may be explained on the basis that Anacardic exhibits neuroprotective potential due to their effects on enhancing cell viability, reducing cell toxicity most probably by reducing excessive calcium influx and suppression of reactive oxygen species as well as by decreasing the expression of proapoptotic caspase 3 gene and increasing the expression of antiapoptotic gene Bcl2. Traditional use in enhancing learning and memory was justified in part by inhibition of Acetylcholinesterase AChE.

Anacardic has several pharmacological actions, such as antioxidants, anticholinesterase, and anti-inflammatory, which are related to the protection against aging disorders. Additionally, the metals copper and zinc are co-factors of antioxidant enzymes that can be associated with Anacardic to improve brain-protective action. A study by da Silva, Pinheiro, Alves et al. (2020) aimed at evaluating the potential of Anacardic metal complexes using copper and zinc chelators to produce potential agents against Alzheimer's disease. Anacardic-Zn and Anacardic-Cu complexes showed better antioxidant action than free Anacardic. In the anti-AChE activity, Anacardic was like the Anacardic-Cu complex. In models using adult zebrafish, no toxicity for Anacardic complexes was found, and in the locomotor model, Anacardic-Cu demonstrated possible anxiolytic (anti anxiety) action. In in silico experiments comparing Anacardic and Anacardic-Cu complex, the coupling energy with the enzyme was lower for the Anacardic-Cu complex, showing better interaction, and also the distances of the active site amino acids with this complex were lower, similar to galantamine, the standard anti-AChE inhibitor. Thus, Anacardic-Cu showed interesting results for more detailed study in experiments related to Alzheimer's disease.

Ljunggren-Rose, Natarajan, Matta, Pandey, Upender, & Sriram (2020) found that Anacardic induces IL-33 and promotes remyelination in CNS. The addition of

anacardic to cultured oligodendrocyte precursor cells (OPCs) rapidly increased expression of myelin genes and myelin proteins, suggesting a direct induction of genes involved in myelination by anacardic.

Epilepsy is a neurological disease affecting people of all ages worldwide. Júnior, Tchekalarova, Atanasova, Machado, Rios, Paz, Găman, Găman, Yele, Shill, Khan, Islam Ali, Mishra, Islam, Mubarak, Lopes, and Melo-Cavalcante (2018) evaluated the anticonvulsant effect of anacardic. They found that Anacardic exhibited significant anticonvulsant and antioxidant activities and reported that Anacardic may be used as a promising natural product for the treatment of epilepsy.

Respiratory Function

The acute respiratory distress syndrome (ARDS) caused by viral pathogens is a worldwide public health emergency. De Lima Gondim, Ferreira, Nogueira, et al. (2021) investigated the effects of anacardic on acute respiratory distress syndrome caused by lipopolysaccharides. Results showed that anacardic was able to prevent changes in lung function and preserve its mechanical properties from containing inflammatory cell infiltrate, collapse of alveoli, and decreased airway resistance, suggesting that this compound may be effective in preventing the acute respiratory distress syndrome caused by viral pathogens.

Carvalho, Annoni, Torres, Durão, Shimada, Almeida, Hebeda, Lopes, Dolhnikoff, Martins, Silva, Farsky, Saldiva, Ulrich, Owen, Marcourakis, Trevisan, Mauad (2013) found Anacardic from cashew nuts ameliorate lung damage induced by exposure to diesel exhaust particles in mice. The biomarkers of inflammatory and antioxidant responses in the alveolar parenchyma, bronchoalveolar lavage fluid (BALF), and pulmonary vessels were investigated. All doses of Anacardic used in the study ameliorated antioxidant enzyme activities and decreased vascular adhesion molecules in vessels, with decreased levels of neutrophils and tumor necrosis factor in the lungs and BALF. The authors demonstrated that Anacardic

supplementation has a potential protective role on oxidative and inflammatory mechanisms in the lungs.

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