

# The Pivotal Neuroinflammatory, Therapeutic and Neuroprotective Role of Alpha-Mangostin

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## Abstract

Alpha-mangostin ( $\alpha$ -MG), one of the key xanthone derivatives, displays a multiplicity of curative qualities like anti-infective, anti-malarial, anticarcinogenic, antidiabetic actions as well as antioxidant properties. Furthermore, it has proven to have neuroprotective, hepatoprotective, and cardioprotective features, of which the anticarcinogenic action is the most auspicious. Additionally, several *in vitro* and *in vivo* analyses confirm that  $\alpha$ -MG partakes in the major stages of tumor growth: initiation, promotion, and progression. Nevertheless,  $\alpha$ -MG services as an inhibitory agent that modulate various enzymes involved in the metabolic activation and excretion of carcinogens, resistance to oxidative damage, and attenuation of inflammatory response. Numerous studies have also implicated  $\alpha$ -MG in central nervous system (CNS) disorders, among which neuroinflammatory disorders and brain cancer are cardinal. Based on these initial studies on  $\alpha$ -MG, we reviewed the pivotal role of  $\alpha$ -MG in neuroinflammatory disorders.

**Keywords:** Mangosteen; Alpha-mangostin; Neuroinflammation; Neuroprotection; Neurodegeneration

## Introduction

Mangosteen (*Garcinia mangostana* L.) is classified under the family Clusiaceae and is recognized as “the queen of fruits” for its pleasant taste [1]. Currently, many food commodities such as dietary supplements, beverages are manufactured from mangosteen fruits are gradually gaining recognition because of

their scientifically proven beneficial role in human well-being [1-3]. The pericarps of mangosteen over the years have been used in various countries in Asia for curative tenacities in disease such as abdominal disorder (e.g. pain, dysentery, and diarrhea), suppuration, infected wounds and chronic ulcers [2, 4]. This pericarp is proven to contain numerous key substances like tannin, xanthone, chrysanthemine, garcinone, gartanin as well as extra bioactive substances [2]. Studies [4, 5] have proven that numerous ingredients are encompassed in the fruit structure of mangosteen and very prominent among them are  $\alpha$ -mangostin ( $\alpha$ -MG),  $\gamma$ -mangostin ( $\gamma$ -MG) and  $\beta$ -mangostin ( $\beta$ -MG). These components of mangosteen, have varied medicinal potentials like anti-histamine action, blockage of the sarcoplasmic reticulum  $\text{Ca}^{2+}$ -pumping adenosine 5-triphosphate (ATP)ase, and anti-serotonin actions [5-8]. Other mangosteen xanthone derivatives includes, 8-hydroxycudraxanthone G, mangostingone, garcinone D, cudraxanthone G, 8-deoxygartanin, garcimangosone B, garcinone E, gartanin, 1-isomangostin, mangostinone, smeathxanthone A, tovophyllin A, 3-isomangostin 8-desoxygartanin and 9-hydroxycalabaxanthone [9-11].

One of the most copious xanthone derivatives from the pericarps of mangosteen is  $\alpha$ -MG. It comprises of 78% of the mangosteen content and it is one of the most investigated chemopreventive phytochemicals [2]. It has proven to have a wide range of medicinal characteristic like antioxidant, anti-infective, anti-malarial, anticarcinogenic, and antidiabetic actions. Furthermore, it has proven to have neuroprotective, hepatoprotective, and cardioprotective features, of which the anticarcinogenic action is the most auspicious [2, 12, 13]. Additionally, several *in vitro* and *in vivo* analyses confirm that  $\alpha$ -MG partakes in the major stages of tumor growth: initiation, promotion, and progression.  $\alpha$ -MG services as an inhibitory agent that modulate various enzymes involved in the metabolic activation and excretion of carcinogens, resistance to oxidative damage, and attenuation of inflammatory response [2]. Moreover, the blockade of cell proliferation via modulating cell cycle regulatory machinery, induction of apoptotic effects on damaged and transformed cells, and inhibition of angiogenic and metastatic processes of tumor cells makes it a potential suppressing agent [2]. For the purposes of our review, we will concentrate on the pivotal role of  $\alpha$ -MG in neuroinflammatory disorders.

## $\alpha$ -MG and Mitochondrial Energetic Metabolism

Studies [14, 15] have demonstrated that  $\alpha$ -MG triggers mito-

Manuscript submitted October 13, 2017, accepted October 20, 2017

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doi: <https://doi.org/10.14740/jnr455w>

chondrial membrane depolarization and cytochrome C secretion in PC12 rat pheochromocytoma cells, which means that  $\alpha$ -MG, stimulates programmed cell death via the mitochondrial pathway. The type of the molecular processes associated with the secretion of cytochrome C which is a cardinal part of mitochondrial apoptotic pathway stimulation still remains a matter of debate [14]. Nevertheless, the mitochondrial permeability transition (mPT), a  $\text{Ca}^{2+}$ -dependent undefined permeabilization mechanism, is frequently linked to this programmed cell death. The mitochondrial permeability transition pore (mPTP) is built from a collection of antecedent proteins, whose action is controlled by  $\text{Ca}^{2+}$ -binding spots on the matrix side of the inner membrane. The alternation of the mPTP from open to closed positions and *vice versa* aids in the secretion  $\text{Ca}^{2+}$  from the matrix in a physiological manner [14, 16]. Conversely, following gigantic  $\text{Ca}^{2+}$  buildup, pore opening leads to pathological effects [17]. The sensitivity of mPT to  $\text{Ca}^{2+}$  is significantly amplified by a variety of triggers and circumstances [14, 18]. Many studies [14, 19, 20] have proven that oxidative stress may lead to mitochondrial nonspecific permeability besides  $\text{Ca}^{2+}$  encumber.

It has been demonstrated in both theoretical and experimental observations that  $\text{Ca}^{2+}$  can augment the production of reactive oxygen species (ROS). Cadenas and Boveris [21] have demonstrated that addition of  $\text{Ca}^{2+}$  and complex III inhibitor (antimycin A) to rat heart mitochondria resulted in sharp augmentation of ROS production. They explained that this phenomenon could perhaps be as a resultant uncoupling effect [21]. Also *in vitro* experiments on isolated brain mitochondria revealed a melodramatic upsurge in generation of ROS by complex I when electron flow from NADH to coenzyme Q was inhibited by rotenone [14, 22]. Studies [14, 23] have demonstrated that in an extraordinary pattern of regulation, the aerobic metabolism, via mitochondrial oxidative phosphorylation, reduces  $\text{O}_2$  to  $\text{H}_2\text{O}$ , while amplifying ATP synthesis and sustains of ROS generation to concentrations obligatory for microdomain cell signaling. The key ROS generated by mitochondria is  $\text{O}_2$ , which is transmuted to  $\text{H}_2\text{O}_2$  by the enzyme superoxide dismutase (SOD). Furthermore,  $\text{H}_2\text{O}_2$  can be converted to OH chaperon by metal ions during the Fenton reaction [14]. Nevertheless, the principal origin of  $\text{O}_2$  is the semiquinone radical intermediate (QH) produced during the Q cycle at complex III, though rotenone and other complex I inhibitors also trigger  $\text{O}_2$  production [14, 24].

Martínez-Abundis et al [14] demonstrated that  $\alpha$ -MG has incomplete protective anti-lipid peroxidation and anti-oxidative damaging effects on proteins. They detected a substantial amplification of peripheral  $\text{H}_2\text{O}_2$  facilitated by  $\alpha$ -MG as well as triggering the activation of aconitase, blockade of respiratory rates and the formation of unspecific mPT. They further stated that the silhouette for the blockade of TBARS generation by  $\alpha$ -MG was coherent with impediment of oxidative modification of mitochondrial proteins. They therefore proposed that the upsurge in  $\text{H}_2\text{O}_2$  generation and inhibition of mitochondrial energetic metabolism implies that concentration-dependent effect of  $\alpha$ -MG on TBARS generation resulted in aconitase activity [14]. Consequently, the site of  $\text{O}_2$  production is pertinent in clarifying this contradictory effect. Nevertheless, in rotenone-inhibited complex I, the potential locus of

$\text{O}_2$  is on the matrix-protruding arm [25]. Thus,  $\text{O}_2$  generation by complex I is usually discharged into the mitochondrial matrix, before  $\alpha$ -MG can be accrued in this compartment [14]. This phenomenon clarifies the irreversible aconitase inhibition pattern.

Martínez-Abundis et al [14] further revealed that  $\alpha$ -MG blocked lipid and protein oxidation and at elevated levels, it similarly possesses damaging consequences on mitochondrial activities. A conceivable justification might be that, as it coexists with several flavonoids, auto-oxidation of  $\alpha$ -MG might produce semiquinone radicals and quinines reducing mitochondrial abilities. Furthermore, quinoid products from mangiferin, a glucosyl xanthone, have the ability to arylate protein thiol groups and to activate the mitochondrial mPT [14, 26]. Also, the interface between semiquinone radicals obtained from  $\alpha$ -MG with oxygen usually leads to reoxidation of the quinone and generation of  $\text{O}_2$  both in the outer and in the inner sides of the internal mitochondrial membrane. Nevertheless, augmented oxidative stress stimulated by quinone-like products of  $\alpha$ -MG might be associated with the detected mutilation of the active metabolism: extricated outcome, ADP-triggered respiration reticence and straight interface with complex IV concentration, likewise the stimulation of the absorbency modification [14].

It is proposed that a blockage on stage three respiration might specify a straight interface with the multiplexes of the respiratory chain. This hypothesis was established by quantifying cytochrome c oxidase action blocked by  $\alpha$ -MG. Furthermore, the hydrophobic attributes of  $\alpha$ -MG and the justification that BSA, and not CSA, blocked the consequence of this compound on mPT stimulation, implies a straight disquieting consequence on the lipidic domain of mitochondria [14]. Moreover, a study by Dorta et al [27] proved that specific flavonoids exercise an extricating activity in mitochondrial membranes. They indicated that the respiratory chain blockade by this flavonoid has also been linked to their redox action, resulting in the production of ROS, thus aiding in the stimulation of mPT. Salvi et al [28] demonstrated that polyphenols such as genistein, facilitated mPT through the production of ROS because it is able to interact with complex I or III in the respiratory chain which implies that  $\alpha$ -MG has possible stimulatory role in amplifying penetrability effects in mitochondria. A study [14] has further demonstrated that mangiferin - a glucosyl xanthone -arguments the liability of calcium triggered penetrability modification in rat liver mitochondria. Nevertheless, another study indicated that quercetin blockes mitochondrial oxygen utilization and triggers calcium secretion via the opening of mPTP [14, 29]. This explains the mechanisms via which  $\text{Ca}^{2+}$ -triggered penetrability modification such as  $\text{O}_2$  generation at the I locus of the respiratory chain as well as of specific electron outflow towards  $\text{O}_2$ , beside the blockage of the electron transport at the level of the NADH dehydrogenase [14, 23].

## $\alpha$ -MG and Microglia

Microglia is the local immune cells in the brain, principally

involved in modulating foreign proteins, cell debris, and numerous antagonistic particles. Stimulation of microglia often leads to modification in cell morphology from a resting ramified shape to an amoeboid profile, associated with sustained secretion of inflammatory neurotoxic agents. Furthermore, stimulation of microglia is recognized as the hallmark of neuroinflammation since proinflammatory cytokines and free radicals are generated by microglia in reaction to neuronal injury or immunological disorders [30]. Studies [30, 31] has shown that based on the probability that microglial stimulation may start a cascade of activities resulting in advancement of neurodegeneration, and functions as a key element that initiate the beginning of the degeneration of nigral dopaminergic neurons, to block the microglial stimulation, associated dopaminergic neurodegeneration is now an interesting approach in Parkinson's disease (PD) management. Nevertheless, inflammatory cytokines such as interleukin (IL)-1b, IL-6, tumor necrosis factor- $\alpha$  (TNF)- $\alpha$ , reactive oxygen species (ROS) and inducible nitric oxide synthase (iNOS) were elevated in cerebrospinal fluid (CSF) of PD patients. Their elevation has further influence on neurons thus the triggering of advanced neurodegeneration [30, 32, 33].

Studies [30, 34, 35] have shown that  $\alpha$ -synuclein, the key constituent of Lewy bodies can trigger neurodegeneration in the accumulated form and partake in microglial stimulation by augmented generation of proinflammatory cytokines, thus causing an assiduous and radical nigral neurodegeneration in PD. Furthermore, modulating the stimulated microglia produced by  $\alpha$ -synuclein may be a key approach for the management of neurodegenerative syndromes. Hu et al [30] demonstrated that  $\alpha$ -MG blocked the  $\alpha$ -synuclein-stimulated proinflammatory cytokines generation, nitric oxide (NO) secretion as well as ROS in principal microglial cells. They further indicated that antioxidant  $\alpha$ -MG could reduce  $\alpha$ -synuclein-triggered ROS generation by blockade of NOX-1. They concluded that  $\alpha$ -MG, which blocked microglial stimulation triggered by  $\alpha$ -synuclein by aiming at NADPH oxidase, may be a therapeutic option in averting PD advancement [30].

## $\alpha$ -MG and Neurotransmitters

Some neurotransmitters have demonstrated to mediate with  $\alpha$ -MG during the pathogenesis of neuroinflammatory disorders. Keys among these neurotransmitters are 5-Hydroxytryptamine (5-HT), histamine, acid sphingomyelinase (aSMase), cholinesterase as well as  $\beta$ -amyloid accumulation.

### Acid sphingomyelinase

Studies [36, 37] have proven that aSMase-ceramide pathway is stringently linked to the pathogenesis of atherosclerosis, which facilitates lipoprotein retention within early atheromata and accelerates lesion advancement. Studies [36, 38] have further confirmed that  $\alpha$ -MG has inhibitory actions on aSMase as well as effective selectivity antagonistic action on neutral sphingomyelinase (nSMase). Consequently, a very few amount  $\alpha$ -MG

cognates have been cloned, and initial structure-activity relationship analysis has been accomplished. Research [36, 39] has shown that the blockade action of benzophenone cognate70 is similar to that of  $\alpha$ -MG, but the cytotoxicity is less than 1/10-corrugates. Structurally, the two prenyl adjacent chains are prerequisite to the secretion of effective and selective blockade action to anti-aSMase. Studies have shown that compound 71 devoid of C-2 prenyl group sustains its action but lessens its selectivity while compound 72 devoid of C-8 prenyl group keeps selectivity, but lessening action. Furthermore, the olefinic moiety is conceivably not obligatory for the anti-aSMase actions, but influence selectivity due to tetrahydro-derivative 12 preserves action, although its selectivity is decreased. Nevertheless, the free hydroxyl groups at C-3 and C-6 locations enhance the anti-aSMase action, which is authenticated by the indolence of diacetyl derivative 34 [36, 39].

### Histamine (H1)

It is well established that histamine is one of the key intermediaries of inflammation. Studies have shown that  $\alpha$ -MG possesses anti-inflammatory actions [7]. This was revealed in a study [40] involving the injection of  $\alpha$ -MG intraperitoneally in normal and bilaterally adrenalectomized rats. These anti-inflammatory actions of  $\alpha$ -MG were proved to be its resultant capability of antagonizing histamine H1 receptor. Normally, the structure of antihistamines comprises of at least one tertiary nitrogen group and an aromatic portion containing two phenyl rings. Almost every antihistamine contains synthetic nitrogen compounds such as pyrilamine, phenothiazine and chlorpheniramine [7]. Studies have shown that 4, 4'-diacetyl curcumin a non-nitrogenous compound blocks the actions of histamine on smooth muscle. This compound does not act on the cellular surface receptor sites for histamine, as most synthetic antihistamine drugs do [7]. BiSkesoy and Onaran [41] demonstrated that  $\alpha$ -MG has lower affinity for the histamine H1 receptor as compared to chlorpheniramine, a typical histamine H1 receptor antagonist (pA 2 8.3). Although the structure of  $\alpha$ -MG does not look like antihistamines,  $\alpha$ -MG possesses the histamine receptor blocking action and blocks directly to the histamine H1 receptor sites. Therefore  $\alpha$ -MG may be the first natural medication that can precisely antagonizes the histamine H1 receptor [7].

### Cholinesterase

Davies and Maloney [42] are the first to put forth the "cholinergic hypothesis" which links learning and memory inabilities to substantial reduction in ACh concentration. It is interesting to note that the present typical medications for Alzheimer's disease (AD) are cholinesterase inhibitors. Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) are two key categories of cholinesterase conscientious to the hydrolysis of ACh as well as controlling of cholinergic neurotransmission activities [36, 43]. It has been proven that [36]  $\alpha$ -MG substantial blocks the actions of both AChE and BChE. Further investigations

using molecular docking analyses proved convincingly that hydrogen bonding and  $\pi$ - $\sigma$  interfaces at the functional location of these two enzymes may perhaps abet in their effectiveness. Studies have demonstrated that AChE intermediate in the dispensation and accumulation of A $\beta$  peptide far above cholinergic actions, which is autonomous to its catalytic active site (CAS) as well as it inter-connection to peripheral anionic site (PAS) [36, 44]. Furthermore,  $\alpha$ -MG though not very effective anti-AChE can function via inhibition of PAS enzyme and stimulate superfluous remunerations besides its blockade action [36, 45].

### 5-Hydroxytryptamine (5-HT)

The neurotransmitter 5-Hydroxytryptamine (5-HT) partakes in various behavioral systems. The initiation of 5-HT<sub>2</sub> receptors in the brain lead to hyperactivity syndromes like head-twitch response (HTR), resting tremor, head weaving and hypertonicity. The most comprehensively investigated behavioral models for the stimulation of 5-HT receptors in the central nervous system is HTR and 5-HT syndrome [46-49]. The 5-HT syndrome comprises of sequences of multifarious behavioral indicators that mostly embrace repetitive tramping of the fore-paws, abduction of the hind limbs, Straub's tail and resting tremor [46, 49]. The HTR and 5-HT syndrome can be induced in mice and rats by injecting 5-HT precursors, tryptophan or 5-HTP [46, 47, 49]. The injection of 5-HT receptor agonists will directly trigger 5-HT receptors like 5-methoxy-N, N dimethyltryptamine or D-lysergic acid diethylamide (LSD) or by drugs that secretes 5-HT like fenfluramine [46, 48].

Studies [46, 50, 51] have shown that these two behavioral models of 5-HT receptor initiation correlate well with distinctive kinds of 5-HT receptor. The HTR in mice is meticulously linked to the activities of 5-HT<sub>2</sub> receptors on postsynaptic neurones, while the 5-HT syndrome is linked to postsynaptic 5-HT<sub>1</sub> receptors [46, 52]. The 5-HT<sub>2</sub> receptors comprises of three distinctive subtypes such as 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub> and 5-HT<sub>2C</sub>. Studies [46, 53, 54] have proven that HTR in mice or rats is the precise behavioral model for the stimulation of 5-HT<sub>2A</sub> receptors. Furthermore, studies [46, 53, 55] have demonstrated that intraperitoneal injection of 5-fluoro-a-methyltryptamine (5-FMT) triggers head-twitches via the stimulation of central 5-HT neurones. Moreover, studies [46, 53] have shown that monoamine oxidase-A blockade via 5-FMT may lead to an upsurge in intracellular concentrations of 5-HT followed by an upsurge in 5-HT secretion. This perhaps lead to an augmented activation of postsynaptic 5-HT<sub>2</sub> receptors [53]. These discoveries signify that 5-FMT-treated animals can be used to investigate the action of 5-HT<sub>2</sub> receptor antagonists on the postsynaptic 5-HT<sub>2</sub> receptors. Recently, studies have demonstrated that  $\gamma$ -MG could be a selective antagonist for 5-HT<sub>2A</sub> receptors in smooth muscle and platelets [7, 46]. Interestingly  $\gamma$ -MG does not have a nitrogen atom but rather possesses marked 5-HT<sub>2A</sub> receptor blocking activity. Currently, no research data linking 5-HT<sub>2A</sub> receptors and  $\alpha$ -MG exist, although several studies have linked 5-HT<sub>2A</sub> receptors and  $\gamma$ -MG. We therefore propose the new research on  $\alpha$ -MG should be geared towards this direction.

### $\beta$ -amyloid

Studies [36, 56] have demonstrated that the generation and build-up of oligomeric masses of A $\beta$  is a fundamental occurrence during the pathogenesis of AD. These masses are assumed to be the triggers of pathogenic cascade leading to neuronal loss and dementia [56]. Further studies have shown that inhibition of these A $\beta$ -masses is a realistic treatment approach that can lessen and/or avert the advancement of AD. Current research has proven that  $\alpha$ -MG exhibits substantial protective effect against neurotoxicity stimulated by A $\beta$ -(1-40) or A $\beta$ -(1-42) oligomers. Also,  $\alpha$ -MG preserves natural morphology of mammalian neurons, enriches their natural biological activities as well as interrupts the extreme advancement of AD [36, 57]. The above attributed is possible because of  $\alpha$ -MG's capability to block the A $\beta$  accumulation cascades. Studies have shown that toxic  $\beta$ -sheet-rich accumulated A $\beta$  oligomers, later-stage A $\beta$  fibrils and suppressor A $\beta$  fibril effectors are usually responsible for the above actions [36].

### $\alpha$ -MG and Autophagy

Autophagic cell death (ACD) is an imperative biological activity observed in all eukaryotic cells [58-62]. ACD is marked with substantial mortification of cellular constituents, such as parts of the cytoplasm and intracellular organelles via intricate intracellular membrane/vesicle reformation and lysosomal hydrolysis [58-60, 63]. Studies [58, 59] have shown that ACD is essential for growth as well as stress antiphons. Furthermore, it has been detected in numerous human disorders such as neurodegenerative, muscular disorders and defiance to pathogens. Moreover, comparable to apoptosis, ACD is inhibited in malignant cancers. Studies have demonstrated that autophagy is triggered in reaction to  $\gamma$  irradiation and several anticancer remedies, specifically in apoptosis-deficient cells [58, 63, 64]. Numerous molecular and cell-signaling pathways have been incriminated in controlling autophagy. These pathways include the BECN1, AMP activated protein kinase (AMPK), mitogen-activated kinase (MAPK), and phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin (PI3K-AKT-mTOR) pathways [58, 65]. Nevertheless, the comprehensive means via which autophagic cell-signaling pathway function is still a matter of debate although numerous authors have demonstrated that autophagy is activated in reaction to countless anticancer medications [58, 66, 67].

Chao et al [58] demonstrated that  $\alpha$ -MG-triggered autophagy. They further explain that ACD was inhibited by 3-MA, Baf A1 as well as shRNA knockdown of beclin-1. Moreover, choosy knockdown of AMPK release by AMPK shRNA reduced  $\alpha$ -MG-triggered autophagy. They again demonstrated that AMPK is responsible for indolent phosphorylation of raptor and relationship between raptor and the inhibitor 14-3-3 $\gamma$ , leading to mTORC1 blockade. Studies [58, 68, 69] have shown that serine or threonine kinase and Liver kinase B1 (LKB1), is the key controller of AMPK via phosphorylation of AMPK at the stimulation loop, precisely at threonine 172 of the  $\alpha$ -subunit. Further studies [58, 68-70] have demonstrated that the stimulation of the LKB/AMPK pathway is related to autophagy. A study [71] has shown that mTOR

complex 1 (mTORC1) is a key controller of autophagy. The mTORC1 complex comprises of the scaffolding protein regulatory-related protein of mTOR (raptor), mammalian lethal Sec13 protein 8 (mLST8), proline-rich Akt substrate 40 kDa (PRAS40), and DEP-domain-containing mTOR-interacting protein (Deptor) [58, 71, 72]. Numerous authors [58, 73-75] have proven that stimulation of mTORC1 is controlled by diverse elements such as PI3K/AKT and AMPK. Furthermore, AMPK can phosphorylate raptor, which is then insulated by 14-3-3 $\gamma$ , leading to mTORC1 blockade [58, 75].

## $\alpha$ -MG and Apoptosis

Studies [2, 76] have proven that there are typically two key apoptotic pathways which are; the extrinsic or death receptor pathway and the intrinsic or mitochondrial pathway. It has been proven that the extrinsic pathway is stimulated when death ligands binds to death receptors on the cell surface resulting in the triggering of caspase-8. On the other hand, the intrinsic pathway is depicted with the loss of mitochondrial membrane potential, resulting in the secretion of cytochrome c and caspase-9 stimulation [76]. Numerous authors [2, 77-79] have demonstrated that  $\alpha$ -MG triggers apoptosis via both the extrinsic and intrinsic pathways resulting in the stimulation of caspases-8, -9 and -3, in human hepatoma SK-Hep-1 cells, melanoma SK-MEL-28 cells and breast cancer MDA-MB-231 cells. Furthermore, a study [80] also revealed the upregulation of Fas and tBid in human colorectal cancer COLO 205 cells. The suggested means via which  $\alpha$ -MG-triggered apoptosis is in the various cancers above is explained below. Treatment of  $\alpha$ -MG with the cell lines resulted in the stimulation of extrinsic pathway which in turn triggered procaspase-8 cleavage into caspase-8. This further leads to cleavage of Bid to tBid. The formed tBid then translocated to mitochondria leading to the stimulation of the mitochondrial apoptotic pathway [2, 80]. Studies [2, 81, 82] have proven that depletion of mitochondrial membrane potential results in reduction in intracellular ATP, downregulation of proapoptotic Bcl-2 and upregulation of antiapoptotic Bax, secretion of cytochrome c from mitochondria into cytosol, stimulation of the caspase cascade, and augmentation of poly (ADP-ribose) polymerase (PARP) cleavage were the main events involved in the mitochondrial apoptotic pathway is triggered by  $\alpha$ -MG.

Numerous authors [83-85] believe that ROS is an interceder during apoptosis signaling. Furthermore, ROS are higher in cells experiencing apoptosis and antioxidants proven to safeguard neuronal cells against apoptosis triggered by a multiplicity of apoptotic mediators. Moreover, ROS trigger caspase-3 and caspase-3-like proteases in different cell categories including neuronal cells, resulting in nuclear compression and DNA disintegration [83, 86-89]. Nevertheless, ROS also trigger apoptosis, possibly by reducing secretion of Bcl-2, an antiapoptotic molecule [83, 90, 91]. Also, Bcl-2 and Bax may regulate the mitochondrial penetrability modification pore, which can instigate the movement of cytochrome c and some apoptosis-triggered dynamics that activate the stimulation of caspase cascade leading to apoptosis [83, 90]. Studies [83, 92] have proven that caspase-3 is associated with apoptotic

activities happening in the mitochondrial-adjunct pathway, which are related to nuclear compression and DNA cleavage. Furthermore, studies [83, 93] have shown that caspase-3 also stimulates phosphatidylserine externalization from the internal to external leaflets of the plasma membrane. Another study [94] indicated that phosphatidylserine appearance on the external leaflet of the plasma membrane enhance its binding to annexin-V which is extensively detected in apoptosis.

Studies [83, 95] have proven that xanthone revolutionizes iodoacetate-triggered cell death in principal cultures of cerebellar granule neurons by decreasing ROS configuration. On the other hand,  $\alpha$ -MG has proven to mitigate the neurotoxicity triggered by beta-amyloid oligomers in SK-N-SH neuroblastoma cells and prime rat cerebral cortical neurons [57, 83, 96]. Studies [83, 97] have further demonstrated that the antioxidative feature of  $\alpha$ -MG is perhaps interceded by its regulatory influence on the movement of glutathione peroxidase. Janhom et al [83] indicated in their study that  $\alpha$ -MG salvages apoptosis in dopaminergic SHSY5Y cells induced with 1-methyl-4-phenylpyridinium (MPP+), a cellular model of PD. They argue further that cytoprotection of  $\alpha$ -MG against MPP+-triggered apoptosis may be linked to the decrease in ROS formation, regulating the stability between pro- and antiapoptotic genes, as well as suppression of caspase-3 stimulation. They demonstrated that DNA staining and PI/annexin-V twofold staining reinforce the notion that  $\alpha$ -MG safeguarded nuclear modifications and phosphatidylserine externalization triggered by MPP+ introduction in SH-SY5Y neuroblastoma cells. Nevertheless,  $\alpha$ -MG reduced caspase-3 stimulation, reduced Bax mRNA secretion, and amplified Bcl-2 mRNA secretion triggered by MPP+ in dopaminergic SH-SY5Y neuroblastoma cells. Nonetheless, a study revealed that cisplatin-triggered apoptotic death resulted in  $\alpha$ -MG mitigated proliferation of p53 secretion triggered by cisplatin [83, 98]. Another study [99] established a correlation between p53 and Bcl-2 family members. Studies [83, 99] have further shown that proapoptotic Bax, straightforwardly triggered by p53, can withstand the antiapoptotic influences of Bcl-2, while p53 can straightforwardly block Bcl-2. Janhom et al [83] also observed that  $\alpha$ -MG may decrease the influences of MPP+ on Bax and Bcl-2 secretion by mitigating p53 secretion. Additional studies [4, 83] have proven that xanthone also blocks brain-derived acidic sphingomyelinase, a protein that regulates apoptosis and cell development.

## Neuroinflammatory Potentials of $\alpha$ -MG

Neuroinflammation is key component in the pathogenesis and advancement of neurodegenerative disorders such as AD, PD, frontotemporal dementia, amyotrophic lateral sclerosis and multiple sclerosis [100-102]. Studies [101-104] have demonstrated that brains from patients with neurodegenerative disorders are depicted with distinct astrocytosis, stimulation of microglia and higher concentrations of proinflammatory cytokines. Further studies [101, 105, 106] have shown that peripheral injection of lipopolysaccharid (LPS) in mice triggers astrocyte and microglia stimulation as well as cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS)

and proinflammatory cytokines secretion in the brain. An *in vitro* study [107] revealed that  $\alpha$ -MG suppresses IL-6 and IL-8 secretion in LPS-triggered human gingival fibroblasts. Nevertheless, studies [101, 108] have proven that IL-6, which was secreted after peripheral immune experimentation, binds to its receptor on brain endothelial cells resulting in upsurge of COX-2 secretion as well as prostaglandin synthesis.

Preclinical statistics and human analyses [101, 109, 110] revealed an imperative role of IL-6 in the pathogenesis of depression, mild traumatic brain injury (TBI) and brief hypoxia. Furthermore, studies [101, 109] have proven that IL-6 is not merely a biomarker of TBI or neuroinflammation but, an intermediary of pathophysiology as well as a key influential factor during neuroinflammatory reaction. Correspondingly, a study [111] has shown that COX-2-catalyzed prostaglandin E2 (PGE2) stimulation IL-6 through p38 mitogen-activated kinase (p38 MAPK) and protein kinase C (PKC). Catorce et al [101] also confirmed an upsurge in COX-2 secretion in the brain. The secretion according to them was principally from cells of blood vessels after LPS induction. Studies [108, 112, 113] have shown that this upsurge could probably be due to IL-6 binding to its receptor as well as intracellular signaling through the c-Jun N-terminal kinase or signal transducer and activator of transcription 3 (JAK/STAT3) pathways. Furthermore, some authors [101, 114] have proven that morphological silhouette of microglia and Iba-1 immunoreactivity was not related to the resultant inflammatory mRNA silhouette after peripheral LPS injection in mice as demonstrated earlier. Nevertheless, Hu et al [30] observed that  $\alpha$ -MG blocks ROS and proinflammatory cytokines generation in  $\alpha$ -synuclein-triggered microglia *in vitro*.

### Inflammatory Signaling Pathways of $\alpha$ -MG

Studies [115, 116] have demonstrated that  $\alpha$ -MG appreciably blocks NO, PGE2, TNF- $\alpha$  and iNOS generation in LPS-triggered RAW 264.7 cells (Fig. 1b). PGE2, TNF- $\alpha$  and iNOS are cytokines implicated in inflammatory activities, such as amplified vascular penetrability, vascular dilation and neutrophil chemotaxis [115, 117]. Studies [115, 118] have further proven that LPS activation of human monocytes triggers numerous intracellular signaling pathways such as I $\kappa$ B kinase (IKK), nuclear factor- $\kappa$ B (NF- $\kappa$ B) pathway as well as three MAPK pathways: extracellular signal-regulated kinases 1 and 2 (ERK1/2), c-Jun N-terminal kinase (JNK) and p38 (Fig. 1a). These signaling pathways in turn trigger a multiplicity of transcription factors such as NF- $\kappa$ B (p50/p65) and activator protein 1 (AP-1; c-Fos/c-Jun), which synchronize the stimulation of numerous genes encoding inflammatory mediators [115, 118]. Nevertheless, the anti-inflammatory molecular consequence of  $\alpha$ -MG is still a matter of debate.

### Prostaglandin E2 and Cyclooxygenase Synthesis by $\alpha$ -MG

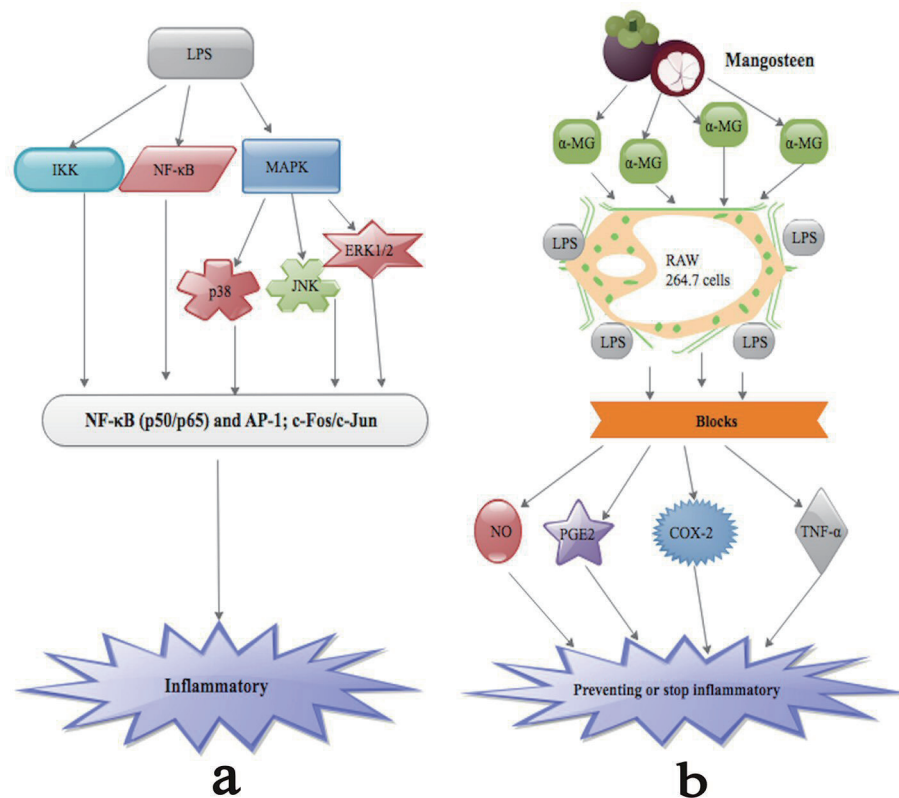
Prostaglandin E2 (PGE2) concentrations are extremely truncated or indiscernible in natural circumstances in the brain, nevertheless can be upsurge in inflammatory circumstances

such as multiple sclerosis (MS), and AIDS-related dementia [5, 119, 120]. Excessive concentrations of PGE2 can interrupt the actions of numerous cell categories, comprising neurons, glial, endothelial cells as well as control microglia/macrophage and lymphocyte activities in inflammatory and immune circumstances [5, 121]. Consequently, the interaction between PGE2 and prevailing factors, such as pro- and anti-inflammatory cytokines, have prospective effect on the aftermath of inflammatory and immune reactions in the central nervous system (CNS). Several studies [5, 121] have proven that there is a strong relationship between the production of prostaglandins (PGs), inflammation, pain, and fever. Studies [5, 122] have further proven that glial cells, which are far more than neurons with a ratio of approximately 10:1 in the brain, offer mutual mechanical and metabolic sustenance of neurons. Glial cells are anticipated to be a key source of PGs in the CNS [122]. It is proposed [5] that modulation of arachidonic acid (AA) metabolism, specifically PGE2 generation, seems advantageous in patients with inflammatory disorders. Nakatani et al [5] demonstrated that blockade of the 40% ethanol mangosteen extract on prostaglandin E2 synthesis is due to  $\alpha$ -MG and  $\gamma$ -MG. Nevertheless, H<sub>2</sub>O extract of mangosteen might have unidentified constituents with inhibitory influence on PGE2 synthesis other than  $\alpha$ -MG and  $\gamma$ -MG, since the extract that had no  $\alpha$ -MG and  $\gamma$ -MG also blocked PGE2 synthesis.

On the other hand, cyclooxygenase (COX) which is rate-limiting enzyme in PG synthesis appears in two isoforms. These two isoforms are the constitutive (COX-1) and the inducible (COX-2). They are derived from different genes, but are structurally preserved [5, 123, 124]. It is proven [5] that COX-1 secretion is developmentally oriented. PGs generated via COX-1 predominantly partake in fluid and electrolyte homeostasis, gastric acid secretion, as well as platelet aggregation. However, COX-2 is secreted in reaction to inflammatory incitements. It is effective in biological reactions to growth factors and glucocorticoids [5, 125]. Navya et al [126] researched into the molecular interface between  $\alpha$ -MG, iNOS and COX-2 using computer docking kits (Fig. 1b). They demonstrated that  $\alpha$ -MG is a ligand against COX-2 and iNOS, correspondingly, and bound the two via hydrogen bond interface. They however did not indicate whether  $\alpha$ -MG can directly act via COX-2 and iNOS [126]. Therefore, further studies are needed in this direction. Nevertheless, as a means responsible for iNOS and COX-2 blockade,  $\alpha$ -MG has proven to trigger SIRT-1, a nicotinamide adenosine dinucleotide-dependent histone deacetylase [2]. Research [127] has shown that SIRT-1 substantially interrelates with the p65/RelA subunit of NF- $\kappa$ B and subdues NF- $\kappa$ B-driven gene transcription via deacetylating p65/RelA at lysine 310. Furthermore, the over secretion of ROS blocks SIRT-1 action via the induction of oxidative adjustments on its cysteine residues, thus augmenting NF- $\kappa$ B signaling leading to inflammatory reactions [2]. Moreover,  $\alpha$ -MG nullified the acetylation of p65/NF- $\kappa$ B and NF- $\kappa$ B-modified proinflammatory gene secretion such as COX-2 and iNOS, via the stimulation of SIRT-1 in the U937 cell line [2, 128].

### Neuroprotective Effect of $\alpha$ -MG

Research [129, 130] has testified that  $\alpha$ -MG has numerous an-



**Figure 1.** (a) LPS activation of human monocytes triggers numerous intracellular signaling pathways such as IκB kinase (IKK), nuclear factor-κB (NF-κB) pathway as well as three MAPK pathways: extracellular signal-regulated kinases 1 and 2 (ERK1/2), c-Jun N-terminal kinase (JNK) and p38. These signaling pathways in turn trigger a multiplicity of transcription factors such as NF-κB (p50/p65) and activator protein 1 (AP-1; c-Fos/c-Jun), which synchronize the stimulation of numerous genes encoding inflammatory mediators leading to inflammation. (b) α-MG appreciably blocks NO, PGE2, TNF-α and iNOS as well as COX-2 generation in LPS-triggered RAW 264.7 cells.

tioxidant qualities. Studies have proven that α-MG lowered the human low-density lipoprotein (LDL) oxidation stimulated via copper or peroxy radical. Studies [129, 131] have further proven that α-MG restrains the reduction of α-tocopherol depletion stimulated via LDL oxidation. Currently, studies [10, 129] have confirmed that α-MG is capable of scavenging peroxynitrite anion (ONOO<sup>-</sup>). Nevertheless, blockade of mitochondrial metabolism via the toxin 3-nitropropionic acid (3-NP) has proven to trigger the initiation of ROS. Moreover, chronic inoculation of this toxin brought about some histopathological, neurochemical and motor modifications linked to Huntington's disease in monkeys and rodents. These activities above incriminate mitochondrial dysfunction and oxidative stress in neurodegenerative disorders [129, 132, 133]. Several authors [129, 134, 135] have established that the production of ROS like superoxide anion (O<sub>2</sub><sup>-</sup>), hydroxyl radicals (OH<sup>•</sup>), and cellular oxidative mutilation occurs in rat striatum after inoculation of 3-NP. Interestingly, oxidative mutilation and the size of the striatal lesion triggered via 3-NP are decreased after antioxidant inoculation [129, 136].

Numerous studies [129, 137] have implicated augmented secretion of hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) in PC12 cells after 3-NP inoculation. Also, mitochondrial O<sub>2</sub><sup>-</sup> production have also been observed after the inoculation of 3-NP in alveolar bronchial

epithelial cells [129, 138]. Nevertheless, ONOO<sup>-</sup> has also been implicated in 3-NP stimulated toxicity [129, 139]. All the above points to the fact that ROS generation and oxidative mutilation via 3-NP stimulated toxicity in neurons and several cell categories. Pedraza-Chaverr et al [129] demonstrated that α-MG has neuroprotective stimulus on 3-NP toxicity in a concentration-dependent manner. They further indicated that the neuroprotective properties of α-MG are possibly due to its capability of scavenging O<sub>2</sub>, O<sub>2</sub><sup>-</sup> and/or ONOO<sup>-</sup>. In confirmation, both O<sub>2</sub><sup>-</sup> and/or ONOO<sup>-</sup> have been implicated in 3-NP-triggered neurotoxicity [129, 134, 139]. Nonetheless, the neuroprotective influence of α-MG against 3-NP is linked with substantial amelioration of ROS generation which was quantifies using the fluorescent markers ethidium and carboxy-DCF. These finding above means that α-MG may be an auspicious multifunctional agent that could be used treat AD, because of its ability to scavenge ROS, metal-chelating, AChE and BChE blockades as well as Aβ accumulation- lessening potentials [36].

## Conclusions

The anti-inflammatory potentials of α-MG in human cells were

initially restricted to bacterial and some viral infections, malarial, cancer, and diabetes with little focus on neuroinflammatory disorders. It is currently well known that  $\alpha$ -MG reduces LPS-triggered secretion of inflammatory genes. Additionally,  $\alpha$ -MG has also proven to partake in mitochondrial energetic metabolism, microglia activation, autophagy as well as apoptosis in the CNS. Recent studies conducted on neuroinflammatory disorders revealed that  $\alpha$ -MG is a promising adjuvants for the treatment of neuroinflammatory disorders since these disorders may alter cellular metabolism of  $\alpha$ -MG and perhaps rise its bioavailability which in turn reduce the inflammatory process. Furthermore,  $\alpha$ -MG has also proven to possess neuroprotective potential although further studies are still warranted to further elucidate these factors. This means that  $\alpha$ -MG could become a very vital agent in preventing neuroinflammatory disorders.

### Author Contributions

SAR is guarantors of integrity of the entire concepts and design. SAR wrote the final manuscript. SPZ contributed in literature search and draft of sections of the manuscript. ZS, JG and HX contributed equally to the intellectual content of the manuscript.

### Conflict of Interest

All the authors declare no conflict of interest.

### Source of Funding

None.

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