Menoufia Veterinary Medical Journal
(MVMJ)

Menoufia Veterinary Medical Journal
https://vmmj.journals.ekb.eg

MVMJ. Vol. 1 (1)

Menoufia University

Applications of Acridine and Gallic Acid

Noha Hemaid[1], Mohamed Ahmed [2], Omnia Al- Shabrawy [3], Mabrouk Abd Eldaim[4,*]

[1] Molecular Biology, Faculty of veterinary Medicine, Menoufia University [2]Biochemistry and Molecular Biology, Faculty of veterinary Medicine, Menoufia University [3] Department of Biochemistry and molecular biology, Faculty of Veterinary Medicine, University of Sadat City, Sadat City, Egypt [4] Biochemistry and molecular biology, Faculty of Veterinary Medicine, Menoufia university, Shibin El-kom, Al Menoufia, Egypt

Key words:
Acridine, Gallic Acid, Anti-inflammatory, Anti-diabetic, α-glucosidase inhibition.

*Correspondence to
nohahemaid@yahoo.com

Article History
Received: 13 May 2025.
Accepted: 28 July 2025

ABSTRACT

Acridine is one of the simple alkaloids found in nature. Acridines are hetero-aromatic compounds, which interact with both nucleic acids and proteins. The targeting of these biopolymers is broadly applied in cancer therapy and gene delivery. Interestingly, due to direct interactions of acridines with various enzymes, acridines can be suitable drugs for treatment of neurodegenerative diseases, inflammation, immunological disorders, protozoal diseases, diabetes, etc. Numerous processes (involve a change in the composition of a substance and also the mechanism by which these changes occur), including reductive alkylation, nucleophilic addition, electrophilic substitution, reduction, oxidation, and photo-alkylation, occur with acridines. Gallic acid (GA) is a very rich in many edible and herbal plants and has an antioxidative and anti-inflammatory effects on some metabolic disorders. To have a better understanding of its antidiabetic properties and its therapeutic important on human health care, the available review supporting the effective properties of GA. This review outlined the uses of acridine and Gallic acid for treatment of different diseases.

1. ACRIDINE

1.1 Introduction

Acridines are hetero-aromatic compounds that were used for treatment of many diseases in the past [1]. Acridines are very soluble in physiological liquids so they used as antiprotozoal and antibacterial drugs. Heinrich Caro and Carl Gräbe in 1870 identified acridine, one of the most well-known and extensively used classes of bioactive agents, from the extract of boiling coal tar [2].

1.2 Method of Acridine extraction and its uses

Acridine is extracted from coal tar by shaking it off with diluted sulphuric acid and then using potassium dichromate to precipitate it out of the sulphuric acid solution. In the last stage, ammonia breaks down the resultant acridine dichromate. Acridine and its derivatives are stable substances with a weakly basic nature. In the past, anti-tumor activity of acridines was attributed to their interactions with nucleic acids; however, the more recent studies favor an explanation based on direct interaction of acridines with biologically important proteins [1]. The development of human society has incorporated acridine drugs to daily life of millions of individuals worldwide [3, 4-5]. Due to their wide variety of pharmacological actions, acridines and their analogues are a significant class of fused heterocyclic rings that contain nitrogen. Analogues of acridine are distinguished by their unique industrial, chemical, physical, and biological uses [6-7]. Because of their effectiveness in treating and preventing a variety of illnesses, including antimalarial [8-9], antitubercular [10],

antiiflammatory [11-12], antiviral [13], anticancer [14-15], antioxidant [15], antimicrobial [15], antidiabetic [16], antiparasitic [15-17], acetylcholinesterase inhibitors [18], and fungicidal activities [19], acridines and their related derivatives are pharmacologically acceptable.

Moreover, acridines have a variety of uses in laser technology, dyes, and as fluorescent materials for the identification of biological molecules. The semi-planar heterocyclic structure of acridines is responsible for these characteristics, and it interacts significantly with several biomolecular targets [15]. Derivatives of acridine, which are present in a variety of marine species and natural plants, have been shown to exhibit a wide range of biological activities [20, 21]. Over the past ten years, a growing understanding of acridines' method of action has led to significant and interesting studies in this heterocyclic family [15].Furthermore, it is significant to highlight that the biological characteristics and selectivities observed are determined by the position and nature of the substituent on the heterocyclic core. Acridine derivatives have been being screened as antidiabetic drugs in recent years, and the results have been encouraging. Acridine's smooth surface mostly aids in intercalation [20]. Because of their lipophilic and hydrophilic balance, acridines can pass through biological membranes and enter the nucleus to carry out their mode of action.

1.3 Applications of Acridine for Treatment of some Diseases

1.3.1 *Alzheimer's And Parkinson's disease*

The accumulation of aberrant protein aggregates in the brain, primarily made up of amyloid-like fibrils, is linked to neurodegenerative disorders. "Diseases of protein misfolding" is a common term used to describe these conditions [1]. Novel insights into the pathophysiology or therapeutic approaches of one neurodegenerative disease may be significant for other neurodegenerative disorders. Future therapeutic approaches are likely to be based on drug linkages that enhance various aspects of cellular and organismal dysfunction, as altering multiple pathways can improve disease-related phenotypes [22]. Alzheimer's and type II diabetes are the most harmful from a social and economic aspect [23, 24]. The symptoms of these two conditions are different [1]. All of these illnesses have one thing in common: usually soluble proteins may accumulate into insoluble forms that can cause harmful deposits in skeletal and muscular tissue as well as in organs like the liver, heart, pancreas, and brain. However, the toxicity is thought to be caused by soluble aggregates from the early stages of the process [1, 25]. Amyloidogenic lysozyme aggregates can be depolymerised by acridine [26]. From the strongest tetrahydroacridines, through spiro-acridines, to planar acridines, the depolymerisation diminishes in a sequential manner. The target-selective artificial proteases could give a treatment option for amyloid disorders such as Alzheimer's disease, prion diseases, and diabetes [27]. In order to model Parkinson's disease, acridines are primarily utilised to induce tremulous jaw movements [1, 28]. There are very few instances of acridine being used to treat Parkinson's disease.

1.3.2 *Diabetic Disease*

The illness profile can shift from neurodegenerative to, for example, type II diabetes if we take into account the aberrant protein's deposition in organs other than the brain, including the pancreas. Acridines can serve as inhibitors of ribosomal protein S6 kinase 1 involved in diseases such as obesity, diabetes and cancer [1]. As we described the target-selective artificial proteases could give a treatment option for amyloid disorders such as diabetes [27]. Formation of pancreatic islet amyloid correlates with occurrence of advanced type II diabetes mellitus. Acridine orange (AO) can inhibit formation of amyloids from human amylin in dose dependent manner [1].

1.3.3 *Antiparasitic, antibacterial and antiviral activity.*

When a particular enzyme for a pathogenic system is inhibited, acridines can play a significant role as potential medications for the eradication of undesirable microorganisms or pathogenic situations. Acridines can therefore be used to treat a

variety of tropical diseases brought on by protozoal parasites, such as African sleeping sickness; antibacterial agents to treat tuberculosis (TB); antiviral agents to treat human immunodeficiency virus (HIV); and failure of the human immune system to suppress either cancer or a severe autoimmune reaction. Furthermore, because of their specific interactions with protozoal enzymes and processes, acridines are among the most effective antiprotozoal medications. [29, 1–30]. Acridines have advantages structures that improve the effectiveness of drug discovery in the field of protozoan diseases [29, 31] because they are less expensive and cause fewer intellectual property challenges.

Although more potent antibiotics like penicillin were eventually found, acridines were once also used to treat bacterial infections [29, 35 - 38]. It is still possible to use some acridines as local antiseptics. Currently, some acridines may be used again due to the growing resistance of microbes to popular antibiotics. Acridines exhibit activity against Gram-negative bacteria, including *Escherichia coli*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*, as well as Gram-positive bacteria, including methicillin-resistant strains of *Bacillus aureus and Bacillus subtilis*. [39]. the biological activity of acridines is linked to the selective inhibition of DNA gyrase in the case of *Mycobacterium smegmatis* and *Mycobacterium tuberculosis* [40]. Additionally, Rzad et al. highlight the potential of acridines as fungicides, specifically against *Candida albicans*, *Candida glabrata*, *Candida krusei*, and *Saccharomyces cerevisiae*. [41]

1.3.4 ***Anticancer activity***

Acridines and their derivatives mainly work by blocking topoisomerase II and interfering with DNA synthesis [32, 33–34]. This scaffold has made it easier to create a wide variety of derivatives with different structures, which has led to a wider range of pharmacological activity linked to these substances. Acridines' selective toxicity has also been used to treat disorders linked to tumours and cancer. Sections on the interactions of acridines with nucleic acids 4 and nucleic acid processing proteins 5.1 have already covered some of these applications. [29, 35, 1–36]. Acridine 173 was able to treat malignant glioma cells and cross the blood–brain barrier [37].

1.3.5. ***Acridines Used for Staining***

Another potent photosensitiser that can both initiate and prevent a spectrum of biological changes and cell development is acridine orange, an acridine-based chemical [42, 43]. Many acridines are utilised to stain proteins [44, 1], lipids, nucleic acids [1–45], and low molecular weight medications including ceftriaxone, fluvoxamine, and isoniazid [46] because they are distinctive chromophores and fluorophores [1, 44]. Increased fluorescence is typically the result of acridine interactions with hydrophobic areas of macromolecules, and this is advantageous for a variety of staining procedures [1]. A variety of fluorophores were created by conjugating acridines with biotin [1].

2. Gallic Acid

2.1 Introduction

Gallic acid (GA) found in many plants, including Chinese gallnut, dogwood, pomegranate, palmate-leaf rhubarb, peony bark, and others. Gallic acid a naturally occurring polyphenolic molecule with a straight forward chemical structure. Anti-inflammatory, antioxidant, antibacterial, and antiviral properties are among its many pharmacological traits [47–48]. It offers a wide range of potential applications for diseases such as cardiovascular disease [49], nervous system diseases [50], diabetes [51], liver fibrosis [52], and tumour growth [53]. Additionally, GA inhibits α-glucosidase and α-amylase, two protein targets implicated in hypoglycemic effects, according to Oboh et al. Gallic acid is therefore thought to contribute to the hypoglycemic impact and could be an active component of diabetes medications [54]. Gallic acid has low solubility in cool water and limited bioavailability during the absorption process [56] frequently discredit its therapeutic usefulness, despite the fact that it has virtually no toxic or adverse effects, even at high dosages [55]. Gallic acid is a naturally occurring phenolic acid that has

been shown to improve glucose absorption and regulate insulin secretion by reducing the inflammatory response in peripheral tissues brought on by STZ-induced hypoglycemia [57]. Gallic acid is an active ingredient in several plants that have been shown to have antidiabetic effects [58]. The prevention of diabetes mellitus is linked to the consumption of fresh fruits, vegetables, and plants that are high in natural antioxidants [59]. Polyphenols generated from plants have a variety of pharmacological characteristics, and in recent years, there has been a lot of interest in learning more about how they work. Gallic acid (GA), an endogenous plant phenol (3, 4, 5-trihydroxybenzoic acid), has drawn a lot of interest due to its strong antihyperglycemic and free radical scavenging properties [57]. Additionally, grapes, berries, fruits, and wine are rich sources of Gallic acid. GA has been shown to have antioxidant, anti-inflammatory, and anti-cancer properties [60].

2.2 Structure

With the molecular formula C6H2 (OH) 3COOH, Gallic acid (GA) is a naturally occurring phenolic acid that is widely dispersed in a variety of food plants, such as tea leaves, oak bark, blueberries, grape seeds, rose flowers, sumac, witch hazel, gall nuts, and Syzygium cumini fruit [61]. The nutritional value of these GA-rich plant products may be influenced by the biological actions of GA and its derivatives. For instance, numerous studies have shown that tea has antioxidant and cholesterol-lowering properties [62]. Phenolic compounds, which have demonstrated a broad range of pharmacological activities regarding antioxidant, anti-inflammatory, and protective properties against severe metabolic disorders, including cardiovascular and neurodegenerative diseases, cancer, hyperlipidaemia, obesity, and diabetes, are primarily responsible for the health benefits of tea. Furthermore, Hibiscus sabdariffa, a refreshing beverage, was shown to include GA and protocatechuic acids as antihyperglycemic principles. It has also been demonstrated that drinking this beverage can help with liver problems, dyslipidaemia, and hypertension.

As an antioxidant and immune-regulating agent against infections, Gallic acid (GA), a naturally occurring phenic acid derived from edible plants, has been used in nutraceutical goods. The primary reason for GA's many health benefits may be its capacity to scavenge free radicals, which aids in the prevention or treatment of OS, a condition that is closely linked to diabetes mellitus and its consequences [63]. GA is frequently produced by hydrolysing polyphenol tannic acid or tannins (gallotannins and ellagitannins) [64]. Furthermore, GA may be produced by enzymatic, biological, acidic, or alkaline mechanisms. Tannic acid could be hydrolysed using an *Enterobacter spp*. inducible hydrolase to produce GA.

2.3 Gallic Acid in Traditional Chinese Medicine

Some therapeutic plants, such as *Terminalia chebula Retz. (Chebulae Fructus), Punica granatum L. (Pomegranate rind),* and *Sanguisorba officinalis L. (Sanguisorbae radix*), have been found to have GA as a bioactive phytochemical component. Following treatment with the accompanying herbal remedy, the host's metabolic profile improves, which is linked to the bioactive actions of GA and its derivatives found in traditional Chinese medicine [65, 66].

2.4 Mechanism of Gallic Acid’s Antioxidant and Anti-Inflammation

The phenolic hydroxyl groups can mediate radical oxidation because they can interact with the benzene ring of molecules that have the capacity to produce free radicals. Furthermore, transition and subtract metal ions that encourage free radical destruction may be chelated by phenolic compounds. In addition to forming hydrogen-bonding contacts, phenolic structures with hydrophobic phenyl rings and phenolic hydroxyl groups may also work in tandem with proteins like cytochrome P450 isoforms, cyclooxygenases, lipoxygenases, and xanthine oxidases. They may thereby prevent the generation of radicals by inhibiting certain oxidative enzymes, such as malondialdehyde (MDA), oxidised low-density lipoproteins (oxLDLs), and advanced oxidation protein products (AOPPs). In addition to its capacity for scavenging, GA may also have pro-oxidative properties [67].

In fact, GA's biological actions may depend on whether it acts as a prooxidant or an antioxidant. By forming stable semiquinone Free Radicals (FRs), GA demonstrated strong antioxidant properties that reduced the deaminating power of FRs. Numerous studies have demonstrated that its strong antioxidant properties of scavenging free radicals are related to oxygen radical absorbance capacity (ORAC), 2,2-diphenyl-1-picrylhydrazyl (DPPH), and ferric-reducing antioxidant power (FRAP) [67].

By avoiding tyrosine nitration, GA's phenolic hydroxyl group allows it to react with reactive nitrogen species (RNS) or Reactive oxygen species (ROS) to prevent the overproduction of damaging FRs, such as peroxyl, hydroxyl, and superoxide radicals, as well as peroxynitrite radicals. Meanwhile, the production of Glutathione (GSH) and Glutathione Peroxidase (GPX) is linked to a process that regulates Oxidative stress (OS). By controlling Carbon catabolite repressor A and Fungal Activator of Riboflavin biosynthesis (CreA and FarB) transcription factors, which are involved in the attenuation of OS through the GSH- and thioredoxin-dependent systems, GA prevented aflatoxin production in Aspergillus flavus [68].

Furthermore, in endothelial cells, delphinidin and its metabolite GA may raise intracellular GSH [69]. GA may be able to stop tissue oxidative damage caused by acute ketamine or dibutylphthalate exposure. In order to prevent cell damage brought on by the negative side effects of cancer radiation therapy, GA demonstrated radio-protective qualities [70]. Addition of GA (100 mg/kg) decreased radiation-induced cellular DNA damage in whole-body irradiation mice's spleenocytes, bone marrow cells, and blood leukocytes. By inhibiting the peroxidation of membrane lipids, GA supplementation repaired the radiation-induced drop in GPX and GSH levels in diverse irradiated mice's tissues, resulting in less weight loss and death following irradiation [71].

Dependent cellular apoptosis, and it is recognised that lung cancer cells triggered by GA By controlling ROS death, which is linked to ROS rise and GSH depletion, GA may be able to stop the proliferation of Hematopoietic cell transplantation-15 (HCT-15) colon cancer cells. By activating nuclear factor erythroid 2-related factor 2 (Nrf2), GA has also been shown to return the inflammatory and antioxidant status to normal [72, 73].

Proptosis and the Nucleotide-binding oligomerization domain, Leucine rich Repeat and Pyrin domain containing3 - NIMA (never in mitosis gene a)-related kinase 7 (NLRP3–NEK7) interaction, which is important on Nrf2 signalling, were both inhibited by GA [74]. The Extracellular signal-Regulated Kinase (ERK)/Nrf2-induced antioxidative signalling pathway may also be modulated by GA, and the possible mechanism suggested that GA may have competed with Nrf2 for binding to Kelch-like ECH-associated protein 1(Keap1) [75]. The effects of GA reduced the levels of Superoxide dismutase (SOD), Catalase (CAT), and glyoxalase1 expression in methylglyoxal-induced diabetic nephropathy and reversed the methylglyoxal-induced changes in albuminuria, MDA, Nrf2, micro RNA 192 (miR-192), and miR-204 overexpression.

2.5 Gallic Acid for Diabetic Therapy

With the ability to regulate inflammation, apoptosis, or oxidative stress in various pathophysiological cases, GA and its derivatives are strong antioxidants and free radical scavengers. Due to its anti-inflammatory and antioxidant qualities, GA has been shown to have anti-hyperglycemic potential [76]. Adipocytes' glucose homeostasis and insulin sensitivity were improved by GA from *E. officinalis* fruit juice [77].

Mechanistically, Glucose Transporter 4 (GLUT4) translocation in adipocytes was facilitated by the simultaneous activation of Peroxisome Proliferator-Activated Receptor (PPAR) and CCAAT/enhancer-binding proteins (C/EBPs). Furthermore, via controlling the Ak strain transforming (Akt) and AMP-activated protein kinase (AMPK) signalling pathways, GA may improve insulin sensitivity, demonstrating that *E. officinalis* fruit juice dual activates Akt and AMPK [77]. The results showed that GA's antidiabetic effect was facilitated by PPAR, Akt, and AMPK activation [78].

Furthermore, GA may have antidiabetic benefits through controlling the expression of Tumor Necrosis Factor (TNF) and adipocytokines, by preventing cellular death linked to caspase-9, GA enhanced cell function. Different oxidative-based diabetes problems, including nephropathy, were caused by advanced glycation end-products/ Advanced Lipoxidation End-products (AGE/ALE). Advanced glycation inhibition could result from GA reversing the effects of glyoxal on renal cell viability reduction, membrane lysis, ROS production, lipid peroxidation, mitochondrial membrane potential collapse, and lysosomal membrane leakage. Through its antioxidative potential in diabetic complications, this polyphenol compound modulated various antidiabetic signalling pathways. In the meantime, GA may alleviate cardiac complications, diabetic nephropathy (DN), and neuropathy, as well as prevent OS-induced liver and renal damage in the diabetic state [78].

2.6 Alpha-glucosidase inhibitory activity of Gallic acid

One kind of glycoside hydrolase that is found in the brush cells of the mucosa of the small intestine is alpha-glucosidase. It is in control of breaking the bond between sugar and non-carbohydrate ligands and/or catalysing the breakdown of polysaccharides and oligosaccharides into a single glucose. One of the more efficient methods for creating an Active Pharmaceutical Ingredient (API) for the treatment of diabetes is to screen for glucosidase inhibitors. It has been found that GA inhibits α-glucosidase [79]. Given that the cocrystal former's (CCF) and GA's hydrogen bond interactions change the α-glucosidase inhibitory activity [80].

1. CONCLUSIONS

Acridines and their equivalents are an important class of fused heterocyclic rings that contain nitrogen because of their diverse range of pharmacological activities. Their distinct industrial, chemical, physical, and biological applications set acridine analogues apart.

Acridine has a flat surface which primarily facilitates intercalation. Acridines can penetrate biological membranes and enter the nucleus to conduct their mode of action due to their balance of lipophilic and hydrophilic.

Gallic Acid (GA) is found in a variety of plants, such as peony bark, dogwood, pomegranates, palmate-leaf rhubarb, Chinese gallnut, and others. GA has a simple chemical structure and is a naturally occurring polyphenolic compound. The pharmacological characteristics of this substance include anti-inflammatory, antioxidant, antibacterial, and antiviral effects.

GA and its derivatives are potent scavengers of free radicals and antioxidants. GA has demonstrated antihyperglycemic potential due to its antioxidant and anti-inflammatory properties.

REFERENCES

1- Ježek, J., Hlaváček, J., & Šebestík, J. (2017). Biomedical Applications of Acridines Derivatives, Syntheses, Properties and Biological Activities with a Focus on Neurodegenerative Diseases /series/4857

2- Adhikari, S., & Mitra, A. K. (2023). Perspective on acridine: a versatile heterocyclic biologically imperative framework. In Journal of the Iranian Chemical Society (Vol. 20, Issue 10, pp. 2399–2455). Springer Science and Business Media Deutschland GmbH /10.1007/s13738-023-02840-8

3- Kumar, R., Kaur, M., Silakari, O.: (2013). Chemistry and biological activities of thioacridines/thioacridones. Mini Rev. Med. Chem. 13, 1220–1230

4- Ehsanian, R., Van Waes, C., Feller, S.M.: (2011). Beyond DNA binding- a review of the potential mechanisms mediating quinacrine’s therapeutic activities in parasitic infections, inflammation, and cancers. Cell. Commun. Signal. 9, art. no. 13

5- Sane, R., Agarwal, S., Elmquist, W.F.: (2012). Brain distribution and bioavailability of elacridar after different routes of administration in the mouse. Drug Metabol. Dispos. 40, 1612–1619

6- X. Lang, X. Luan, C.Gao, Y. Jiang, (2012). Recent progress of acridine derivatives with antitumor activity, Prog. Chem. 24, 1497–1505.

7- P. Prasher, M. Sharma, (2018). Medicinal Chemistry of acridine, Medchemcomm 9, 1589–1618.

8- V. Tomar, G. Bhattacharjee, S.Rajakumar Kamaluddin, K. Srivastava, S.K. Puri, (2010). Synthesis of new chalcone derivatives containing

acridinyl moiety with potential antimalarial activity, Eur. J. Med. Chem. 45, 745–751.

9- X.M. Yu , F. Ramiandrasoa , L. Guetzoyan , B. Pradines , E. Quintino , D. Gadelle , P. Forterre , T. Cresteil , J.P. Mahy , S. Pethe , (2012). Synthesis and biological evaluation of acridine derivatives as antimalarial agents, ChemMedChem 7, 587–605.

10- G.C. Muscia, G.Y. Buldain, S.E. Asis, (2014). Design, synthesis and evaluation of acridine and fused-quinoline derivatives as potential anti-tuberculosis agents, Eur.J. Med. Chem. 73, 243–249.

11- L. Mallu, D. Thirumalai, I.V. Asharani, (2017). One-pot cascade synthesis and in vitro evaluation of anti-inflammatory and antidiabetic activities of S-methylphenyl substituted acridine-1, 8-diones, Chem. Biol. Drug Des. 90, 520–526.

12- M.G. Kowalewska, G. Cholewinski, K. Dzierzbicka, (2017). Recent developments in the synthesis and biological activity of acridine/acridone analogues, RSC Adv. 7, 15776–15804.

13- M. Tonelli , G. Vettoretti , B. Tasso , F. Novelli , V. Boido , F. Sparatore , B. Busonera , P.Farci Ouhtit , S. Blois , G. Giliberti , P. La Colla , (2011). Acridine derivatives as anti BVDV agents, Antivir. Res. 91, 133–141.

14- S. Arya , A. Kumar , N. Kumar , P. Roy , S.M. Sondhi , (2015). Synthesis and anticancer activity evaluation of some acridine derivatives, Med. Chem. Res. 24, 1942–1951.

15- Angajala, G., Aruna, V., Pavan, P., & Reddy, P. G. (2021). Ultrasound promoted montmorillonite K-10 catalyzed synthesis, characterization, molecular modelling, SAR and hypoglycemic studies of new rhodanine bejeweled acridine analogues. Journal of Molecular Structure, 1242.

16- M. Mohammadi-Khanaposhtani , S. Rezaei , R. Khalifeh , S. Imanparast , M.A. Faramarzi , S. Bahadorikhalili , M. Safavi , F. Bandarian , E. Nasli Esfahani , M. Mahdavi , B. Larijani , (2018). Design, synthesis, docking study, a-glucosidase inhibition, and cytotoxic activities of acridine linked to thioacetamides as novel agents in treatment of type 2 diabetes, Bioorg. Chem. 80, 288–295.

17- C. Gao , S. Li , X. Lang , H. Liu , F. Liu , C. Tan , Y. Jiang , (2012). Synthesis and evaluation of 10-(3, 5-dimethoxy) benzyl-9(10H)-acridone derivatives, Tetrahedron 68, 7920–7925.

18- S. Hamulakova , J. Imrich , L. Janovec , P. Kristian , I. Danihel , O. Holas , M. Pohanka , S. Bohm , M. Kozurkova , K. Kuca , (2014). Novel tacrine/acridine anticholinesterase inhibitors with piperazine and thiourea linkers 70, 435–439.

19- I. Gabriel, (2020). Acridines as a New Horizons in Antifungal Treatment, Molecules 25, 1480.

20- G. Angajala , V. Aruna , R. Subashini , (2020). An efficient Nano-Copper catalyzed base-free Knoevenagel condensation: A facile synthesis, molecular modelling simulations, SAR and hypoglycemic studies of new quinoline tethered acridine analogues as PPARg agonists, J. Mol. Struct. 1220, 128601.

21- M. Karelou , V. Kourafalos , A.P. Tragomalou , P. Marakos , N. Pouli , O.E. Tsitsilonis , E. Gikas , I.K. Kostakis , (2020). Synthesis, Biological Evaluation and Stability Studies of Some Novel Aza-Acridine Amino derivatives, Molecules 25, 4584

22- Giorgini, F.: (2013). Understanding neuronal dysfunction and loss in neurodegenerative disease. J. Mol. Med. 91(6), 651–652

23- Menting, J.G., Whittaker, J., Margetts, M.B., Whittaker, L.J., Kong, G.K.W., Smith, B.J., Watson, C.J., Zakova, L., Kletvikova, E., Jiracek, J., Chan, S.J., Steiner, D.F., Dodson, G.G., Brzozowski, A.M., Weiss, M.A., Ward, C.W., Lawrence, M.C.: (2013). How insulin engages its primary binding site on the insulin receptor. Nature 493(7431), 241–245

24- Van Exel, E., Eikelenboom, P., Comijs, H., Deeg, D., Stek, M., Westendorp, R.: (2014). Insulin-like growth factor—1 and risk of late-onset Alzheimer's disease: findings from a family study. Neurobiol. Aging 35(3), 725.e7–725.e10

25- Ripoli, C., Piacentini, R., Riccardi, E., Leone, L., Li Puma, D.D., Bitan, G., Grassi, C.: (2013). Effects of different amyloidβ-protein analogues on synaptic function. Neurobiol. Aging 34(4),1032 1044

26- Antosova, A., Chelli, B., Bystrenova, E., Siposova, K., Valle, F., Imrich, J., Vilkova, M., Kristian, P., Biscarini, F., Gazova, Z.: (2011). Structure-activity relationship of acridine derivatives to amyloid aggregation of lysozyme. Biochim. Biophys. Acta 1810(4), 465–474

27- Suh, J.: Progress in designing artificial proteases: (2014). A new therapeutic option for amyloid diseases. Asian J. Org. Chem. 3(1), 18–32

28- Koganemaru,G.,Abe,H.,Kuramashi,A.,Ebihara,K.,Matsuo,H.,Funahashi,H.,Yasuda,K., Ikeda, T., Nishimori, T., Ishida, Y.: (2014). Effects of

cabergoline and rotigotine on tacrine-induced tremulous jaw movements in rats. Pharmacol. Biochem. Behav. 126, 103–108

29- Kumar, R., Kaur, M., Silakari, O.: (2013). Chemistry and biological activities of thioacridines/thioacridones. Mini Rev. Med. Chem. 13, 1220–1230

30- Zhang, B., Li, X., Li, B., Gao, C.M., Jiang, Y.Y.: (2014). Acridine and its derivatives: a patent review (2009–2013). Expert Opin. Ther. Patents 24(6), 647–664

31- Bongarzone, S.,Bolognesi,M.L.: (2011). The concept of privileged structure sinrational drug design: focus on acridine and quinolone scaffolds in neurodegenerative and protozoan diseases. Expert Opin. Drug Discov. 6(3), 251–268

32- S.L. Albino, W.C. da Silva Moura, M.M.L. dos Reis, G.L.S. Sousa, P.R. da Silva, M. G.C. de Oliveira, T.K. dos S. Borges, L.F.F. Albuquerque, S.M.V. de Almeida, M. do C.A. de Lima, S.A.S. Kuckelhaus, I.J. dos S. Nascimento, F.J.B.M. Junior, T.G. da Silva, R.O. de Moura, (2023). ACW-02 an Acridine Triazolidine Derivative Presents Antileishmanial Activity Mediated by DNA Interaction and Immunomodulation, Pharmaceuticals. 16, 204.

33- A. Mr´ oz, I. Ryska, H. Sominko, A. Bejrowska, Z. Mazerska, Drug-drug interaction potential of antitumor acridine agent C-1748: (2018). The substrate of UDP- glucuronosyl transferases 2B7, 2B17 and the inhibitor of 1A9 and 2B7, Pharmacol. Reports. 70, 972–980.

34- R. Briggs, S.P. Kennelly, D. O'Neill, (2016). Drug treatments in Alzheimer's disease, Clin. Med. (Northfield. Il). 16, 247–253.

35- Gensicka-Kowalewska, M., Cholewinski, G., Dzierzbicka, K.: (2017). Recent developments in the synthesis and biological activity of acridine/acridone analogues. RSC Adv. 7, 15776–15804

36- Akhtar, J., Khan, A.A., Ali, Z., Haider, R., Yar, M.S.: (2017). Structure-activity relationship (SAR) study and design strategies of nitrogen-containing heterocyclic moieties for their anticancer activities. Eur. J. Med. Chem. 125, 143–189

37- Teitelbaum, A.M., Gallardo, J.L., Bedi, J., Giri, R., Benoit, A.R., Olin, M.R., Morizio, K.M., Ohlfest, J.R., Remmel, R.P., Ferguson, D.M.: (2012). 9-Aminoacridine pharmacokinetics, braindistribution, and in vitro/in vivo efficacy against malignant glioma. Cancer Chemother. Pharmacol. 69(6), 1519–1527

38- Zhang, B., Li, X., Li, B., Gao, C.M., Jiang, Y.Y.: (2014). Acridine and its derivatives: a patent review (2009–2013). Expert Opin. Ther. Patents 24(6), 647–664

39- D. Walunj, K. Egarmina, H. Tuchinsky, O. Shpilberg, O. Hershkovitz-Rokah, F. Grynszpan, G. Gellerman, (2021). Expedient synthesis and anticancer evaluation of dual-action 9-anilinoacridine methyl triazene chimeras, Chem. Biol. Drug Des. 97, 237–252.

40- B. Zhang, X. Li, B. Li, C. Gao, Y. Jiang, (2014). Acridine and its derivatives: a patent review (2009–2013), Expert Opin. Ther. Pat. 24, 647–664.

41- L. Huo, X. Liu, Y. Jaiswal, H. Xu, R. Chen, R. Lu, Y. Nong, L. Williams, Y. Liang, Z. Jia, (2022). Design and Synthesis of Acridine-Triazole and Acridine-Thiadiazole Derivatives and Their Inhibitory Effect against Cancer Cells, Int. J. Mol. Sci. 24, 64.

42- J.R. Lakowicz, (2006). Principles of Fluorescence Spectroscopy (Springer,. https://doi.org/10.1007/978-0-387-46312-4

43- A.M. Amado, W.M. Pazin, A.S. Ito, V.A. Kuzmin, I.E. Borissev itch, Biochim. Biophys. (2017). Acta Gen. Subj. 1861, 900–909 /10.1016/j.bbagen.2017.01.023

44- Zawada, Z., Šafaˇrík, M., Dvoˇráková, E., Janoušková, O., Bˇ rezinová, A., Stibor, I., Holada, K., Bouˇr, P., Hlaváˇ cek, J., Šebestík, J.: (2013). Quinacrine reactivity with prion proteins and prion-derived peptides. Amino Acids 44(5), 1279–1292

45- Zhang, B., Li, X., Li, B., Gao, C.M., Jiang, Y.Y.: (2014). Acridine and its derivatives: a patent review (2009–2013). Expert Opin. Ther. Patents 24(6), 647–664

46- Abolhasani, J., Hassanzadeh, J.: (2014). Potassium permanganate-acridine yellow chemiluminescence system for the determination of fluvoxamine, isoniazid and ceftriaxone. Luminescence 29(8), 1053–1058

47- K. Li, G. Guan, J. Zhu, H. Wu, Q. Sun, (2019). Antibacterial activity and mechanism of a laccase-catalyzed chitosan-gallic acid derivative against escherichia coli and sta phylococcus aureus, Food Control 96, 234–243.

48- M.G. Salas, A.R. Estilla, J.M. Chávez, S.L. Sepúlveda, R.R. Herrera, C.A. González, (2014). P420 gallic acid has antiviral effect against hepatitis C virus (HCV), which is mediated by its antioxidant activity, J. Hepatol. 60, S208.

49- T.O. Ajibade, A.A. Oyagbemi, T.O. Omobowale, E.R. Asenuga, J.M. Afolabi, A.A. Adedapo, (2016). Mitigation of diazinon-induced

cardiovascular and renal dysfunction by gallic acid, Interdiscip. Toxicol. 9, 66–77.

50- A. Abdel-Moneim, A.I. Yousef, S.M.A. El-Twab, E.S.A. Reheim, M.B. Ashour, (2017). Gallic acid and p-coumaric acid attenuate type 2 diabetes-induced neurodegeneration in rats, Metab. Brain Dis. 32, 1279–1286.

51- A. Abdel-Moneim, S.M.A. El-Twab, A.I. Yousef, E.S.A. Reheim, M.B. Ashour, (2018). Modulation of hyperglycemia and dyslipidemia in experimental type 2 diabetes by gallic acid and p-coumaric acid: The role of adipocytokines and PPARγ, Biomed. Pharmacother. 105, 1091–1097.

52- N.M. El-Lakkany, W.H. El-Maadawy, S.H. Seif el-Din, S. Saleh, M.M. Safar, S.M. Ezzat, O.A. Hammam, (2019). Antifibrotic effects of gallic acid on hepatic stellate cells: In vitro and in vivo mechanistic study, J. Tradit. Complement. Med. 9, 45–53.

53- T.A. Guimaraes, L.C. Farias, C.A. Fraga, J.D. Feltenberger, G.A. Melo, R.D. Coletta, S.H.S. Santos, A.M.B. de Paula, A.L. Guimaraes, (2016). Evaluation of the antineoplastic activity of gallic acid in oral squamous cell carcinoma under hypoxic conditions, Anti-cancer Drugs 27, 407–416.

54- G. Oboh, O.B. Ogunsuyi, M.D. Ogunbadejo, S.A. Adefegha, (2016). Influence of gallic acid on α-amylase and α-glucosidase inhibitory properties of acarbose, J. Food Drug Anal. 24, 627–634.

55- B.C. Variya, A.K. Bakrania, P. Madan, S.S. Patel, (2019). Acute and 28-days repeated dose sub-acute toxicity study of gallic acid in albino mice, Regul. Toxicol. Pharm. 101, 71–78.

56- H.H. Ahmed, A.F. Galal, A.B. Shalby, A.A. Abd-Rabou, F.M. Mehaya, (2018). Improving anti-cancer potentiality and bioavailability of gallic acid by designing Polymeric nanocomposite formulation, Asian. Pac. J. Cancer. P. 19, 3137-3146. doi: 10. 31557/apjcp.2018.19.11.3137.

57- Punithavathi VR, Stanely Mainzen Prince P, Kumar MR, Selvakumari CJ. (2011). Antihyperglycaemic, antilipid peroxidative and antioxidant effects of gallic acid on streptozotocin induced diabetic Wistar rats. Eur J Pharmacol 650: 465–71.

58- Latha RCR, Daisy P. Insulin-secretagogue, (2011). antihyperlipidemic and other protective effects of gallic acid isolated from Tewminalia bellerica Roxb. in streptozotocin-induced diabetic rats. Chem Biol Interact; 189:112–8.

59- Pranprawit A, Heyes JA, Molan AL, Kruger MC. (2015). Antioxidant activity and inhibitory potential of blueberry extracts against key enzymes relevant for hyperglycemia. J Food Biochem; 39:109–18.

60- Patel SS, Goyal RK. (2011). Cardioprotective effects of gallic acid in diabetes-induced myocardial dysfunction in rats. Pharma cognosy Res; 3:239–45.

61- Chhikara, N.; Kaur, R.; Jaglan, S.; Sharma, P.; Gat, Y.; Panghal, A. (2018). Bioactive compounds and pharmacological and food applications of Syzygium cumini-A review. Food Funct, 9, 6096–6115.

62- Naveed, M.; BiBi, J.; Kamboh, A.A.; Suheryani, I.; Kakar, I.; Fazlani, S.A.; FangFang, X.; Kalhoro, S.A.; Yunjuan, L.; Kakar, M.U.; et al. (2018). Pharmacological values and therapeutic properties of black tea (Camellia sinensis): A comprehensive overview. Biomed. Pharmacother. 100, 521–531.

63- Cepas, V.; Collino, M.; Mayo, J.C.; Sainz, R.M. (2020). Redox Signaling and Advanced Glycation Endproducts (AGEs) in Diet-Related Diseases. Antioxidants, 9, 142.

64- Andrade, P.M.L.; Baptista, L.; Britto, J.S.; Uetenabaro, A.P.T.; Costa, A.M.D. (2018). Co-production of tannase and gallic acid by a novel Penicillium rolfsii (CCMB 714). Prep. Biochem. Biotechnol. 48, 700–706.

65- Seo, C.S.; Jeong, S.J.; Yoo, S.R.; Lee, N.R.; Shin, H.K. (2016). Quantitative Analysis and In vitro Anti-inflammatory Effects of Gallic Acid, Ellagic Acid, and Quercetin from Radix Sanguisorbae. Pharmacogn. Mag. 12, 104–108.

66- Liu, M.P.; Liao, M.; Dai, C.; Chen, J.F.; Yang, C.J.; Liu, M.; Chen, Z.G.; Yao, M.C. (2016). Sanguisorba officinalis L synergistically enhanced 5-fluorouracil cytotoxicity in colorectal cancer cells by promoting a reactive oxygen species-mediated, mitochondria-caspase dependent apoptotic pathway. Sci. Rep. 6, 34245.

67- Velderrain-Rodriguez, G.R.; Torres-Moreno, H.; Villegas-Ochoa, M.A.; Ayala-Zavala, J.F.; Robles-Zepeda, R.E.; Wall-Medrano, A.; Gonzalez-Aguilar, G.A. (2018). Gallic Acid Content and an Antioxidant Mechanism Are Responsible for the Antiproliferative Activity of 'Ataulfo' Mango Peel on LS180 Cells. Molecules 23, 695.

68- Zhao, X.; Zhi, Q.-Q.; Li, J.-Y.; Keller, N.P.; He, Z.-M. (2018). The Antioxidant Gallic Acid Inhibits Aflatoxin Formation in Aspergillus f lavus by Modulating Transcription Factors FarB and CreA. Toxins 10, 270.

69- Goszcz, K.; Deakin, S.J.; Duthie, G.G.; Stewart, D.; Megson, I.L. (2017). Bioavailable

Concentrations of Delphinidin and Its Metabolite, Gallic Acid, Induce Antioxidant Protection Associated with Increased Intracellular Glutathione in Cultured Endothelial Cells. Oxidative Med. Cell. Longev. 2017, 9260701.

70- Fischer, N.; Seo, E.-J.; Efferth, T. (2018). Prevention from radiation damage by natural products. Phytomedicine 47, 192–200.

71- Nair, G.G.; Nair, C.K.K. (2013). Radioprotective effects of gallic acid in mice. BioMed Res. Int. 2013, 953079.

72- Zhou, D.; Yang, Q.; Tian, T.; Chang, Y.; Li, Y.; Duan, L.-R.; Li, H.; Wang, S.-W. (2020). Gastroprotective effect of gallic acid against ethanol-induced gastric ulcer in rats: Involvement of the Nrf2/HO-1 signaling and anti-apoptosis role. Biomed. Pharmacother. 126, 110075.

73- Radan, M.; Dianat, M.; Badavi, M.; Mard, S.A.; Bayati, V.; Goudarzi, G. (2019). In vivo and in vitro evidence for the involvement of Nrf2-antioxidant response element signaling pathway in the inflammation and oxidative stress induced by particulate matter (PM10): The effective role of gallic acid. Free Radic. Res. 53, 210–225.

74- Lin, Y.; Luo, T.; Weng, A.; Huang, X.; Yao, Y.; Fu, Z.; Li, Y.; Liu, A.; Li, X.; Chen, D.; et al. (2020). Gallic Acid Alleviates Gouty Arthritis by Inhibiting NLRP3 Inflammasome Activation and Pyroptosis Through Enhancing Nrf2 Signaling. Front. Immunol. 11, 580593.

75- Ha,A.W.; Kim, W.K. (2017). Antioxidant mechanism of black garlic extract involving nuclear factor erythroid 2-like factor 2 pathway. Nutr. Res. Pract. 11, 206–213.

76- D'Souza, J.J.; D'Souza, P.P.; Fazal, F.; Kumar, A.; Bhat, H.P.; Baliga, M.S. (2014) Anti-diabetic effects of the Indian indigenous fruit Emblica officinalis Gaertn: Active constituents and modes of action. Food Funct. 5, 635–644.

77- Variya, B.C.; Bakrania, A.K.; Patel, S.S. (2020). Antidiabetic potential of gallic acid from Emblica officinalis: Improved glucose transporters and insulin sensitivity through PPAR-and Akt signaling. Phytomedicine 73, 152906.

78- Bak, E.J.; Kim, J.; Jang, S.; Woo, G.H.; Yoon, H.G.; Yoo, Y.J.; Cha, J.H. (2013). Gallic acid improves glucose tolerance and triglyceride concentration in diet-induced obesity mice. Scand. J. Clin. Lab. Investig. 73, 607–614.

79- G. Oboh, O.B. Ogunsuyi, M.D. Ogunbadejo, S.A. Adefegha, (2016). Influence of gallic acid on α-amylase and α-glucosidase inhibitory properties of acarbose, J. Food Drug Anal. 24, 627–634.

80- N. Xue, Y.T. Jia, C.W. Li, B.N. He, C.Q. Yang, J. Wang, (2020).Characterizations and assays of α-glucosidase inhibition activity on gallic acid cocrystals: can the cocrystals be defined as a new chemical entity during binding with the α-glucosidase? Molecules 25, 1163.