Bulletin of University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca. Food Science and Technology
Open Access

Gallic Acid: Derivatives and Biosynthesis, Pharmacological and Therapeutic Effect, Biological Activity

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REVIEW

Abstract

Phenolic compounds are important compounds responsible for many therapeutic, pharmacological, and biological activities. They are compounds that do not have nutritional properties but are very important from a medical point of view. In this review, general properties, derivatives and biosynthesis, pharmacological and therapeutic effects, biological activities, and toxic and side effects of gallic acid were reviewed. As a result of the literature research, it has been seen that it has pharmacological and therapeutic effects such as gastrointestinal diseases, cardiovascular disease, neuropsychological and neuroprotective conditions, metabolic diseases, allergic skin, antianxiety, wound healing activity, rheumatoid arthritis, colitis, obesity. It has also been reported to have biological activities such as antioxidant, anti-melanogenic, antimicrobial, anti-ageing, antidiabetic, antiapoptotic, anticancer, anti-inflammatory, hepatoprotective, antiviral, cytotoxic, antidepressant. In this context, it has been determined that gallic acid is an important phenolic compound.

Keywords: biological activity; biosynthesis; gallic acid; pharmacology; phenolic compounds.

Received: 28 August 2023
Accepted: 12 February 2024
Published: 15 May 2024

DOI:
10.15835/buasvmcn-fst:2023.0017

INTRODUCTION

Natural products are faced with many external factors in their living environments (Mohammed et al., 2022). They produce many secondary metabolites as a defense mechanism against these factors. Especially plants are the direct source of many secondary metabolites. In many parts of the world, plants have different uses (Sevindik et al., 2017). Many studies have shown that plants have different activities such as anticancer, antioxidant, antimicrobial, anti-inflammatory, antiproliferative, hepatoprotective, DNA protective (Unal et al., 2022; Aurori et al., 2023; Mohammed et al., 2023a; Has et al., 2023; Uysal et al., 2023). These biological activities occur thanks to the bioactive compounds found in plants (Korkmaz et al., 2021). Phenolic compounds are defined as compounds containing one or more aromatic rings in their structure. Phenolic compounds, also known as secondary metabolites, contain one or more hydroxyl groups in their structure (Budău et al., 2022). Secondary metabolites, also known as phytochemicals, are compounds synthesized by natural processes that protect plants against stress conditions, insects and other pests, microorganisms and

other abiotic factors (Călinoiu et al., 2018; Sevindik et al., 2023a). There are more than 30.000 phenolic compounds produced by plants as a defense mechanism in nature. These phenolic compounds differ according to the structure, number, location and number of the aromatic rings they have, and the bonds they make with other organic compounds (Martău et al., 2023; Pop et al., 2023). Phenolic compounds, as highly complex substances, commonly found in the plant kingdom (galic acid, caffeic acid, stilbenes, flavonoids and polymers, etc.) components (Daglia et al., 2014).

Gallıc acıd and ıts propertıes

Gallic acid, also known as 3,4,5-trihydroxybenzoic acid or gallate, is a phenolic compound in the form of a slightly colorless or slightly yellow crystalline solid at room conditions, which is very important for the formation of tannins. Due to its polar structure, the molecular weight of the compound dissolved in polar solvents such as water, diethyl ether, ethyl alcohol, and glycerol. Its molecular weight is 170.11954 g/mol and its molecular formula is $C_7H_6O_5$. The compound has 3 OH groups placed at the 3', 4' and 5'- positions (Figure 1). Gallic acid, which has a melting point of 210 °C, decomposes when heated up to 235 and 240 0C, releasing carbon dioxide and carbon monoxide. The density of gallic acid is 1.69 kg/L, its pKa is 4.40 and its Log P value is 0.70. Gallic acid, which has an important place in phenolic compounds, also called secondary metabolites, is abundant in grapes, tea, sumac thuja and oak trees (Kim, 2007; Battestin et al., 2008; Nayeem et al., 2016; Rajan and Muraleedharan, 2017; Choubey et al., 2018).

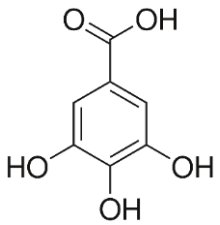

Figure 1. Molecular formula of gallic acid

Gallic acid derivatives and biosynthesis

Tannins are very important for gallic acid. Tannins are very common in the plant kingdom. These common tannins are important both for the growth of the plant and for predators etc. They have duties such as protection against external factors. Apart from this feature, tannins are used in many different sectors for different purposes. Among these sectors; Advanced application areas such as the leather processing industry, mineral adsorption and protein precipitation process, 3D printing and biomedical devices, in iron gall ink production, adhesive production in wood-based industry, anti-corrosion chemical production, uranium recovery chemical from seawater and removal of mercury and methylmercury from solution There are situations like this. Tannins are chemical components that make up a large class of phenolic compounds and have two important groups: those that can be hydrolyzed and those that are condensed tannins. It contains hydrolysable tannins, gallotannins, ellagitannins, and D glucose. Among the concentrated tannins, the most important structure is flavones. Flavones are widespread in nature everywhere in terms of structure. It is also a very diverse group of natural products. Additionally, flavones are a type of polyphenolic compounds containing a C6-C3-C6 flavone skeleton. Tannins; It is abundant in foods such as spinach, coffee, grapes, raisins, dates, tea, chocolate and bananas. Gallic acid is found in plants in a free form or conjugated in tannins. It can be obtained by solvent extraction from plants such as *Quercus infectoria* G.Olivier*, Rhus javanica* (L.) Merr., *Quercus stenophylla* Blume and *Camellia sinensis* (L.) Kuntze. There are also some pathways for the formation of gallic acid (Yang and Wang, 1993; Constable et al., 1996; Arce et al., 1998; Blanko et al., 1998; Chung et al., 1998; Chen and Chung, 2000; Niho et al., 2001; Schofield et al., 2001; Wu et al., 2004; Fernandes and Salgado, 2016; Das et al., 2020). The three most important of these formation pathways are shown below.

A. Phenylalanine → Caffeic acid → 3,4,5 trihydroxycinnamic → 3,4,5 trihydroxybenzoic acid

B. 3,4,5 trihydroxycinnamic → 3,4,5 trihydroxybenzoic acid

C. Shikimic acid → Gallic acid.

Pharmacological and therapeutic effects

The findings in the literature on the pharmacological and therapeutic effects of gallic acid are shown in Table 1. Pharmacological and therapeutic status of gallic acid; It has been shown to be effective on gastrointestinal diseases, cardiovascular disease, neuropsychological and neuroprotective conditions, metabolic diseases, allergic skin,

antianxiety, wound healing, rheumatoid arthritis, colitis and obesity. In case of neuroprotection, it is determined that it depends on their molecular polarity rather than their antioxidant activity in the human SH-SY5Y cell line, and that compounds with high antioxidant activity and appropriate hydrophobicity are generally more effective in preventing oxidative stress damage in neurodegenerative diseases (Lu et al., 2006; Nagpal et al., 2012; Mansouri et al., 2013; Kahkeshani et al., 2019; Mori et al., 2020).

Table 1. Pharmacological and therapeutic effects of gallic acid

Effects	References
Gastrointestinal diseases	Prasad et al., 2010; Kahkeshani et al., 2019
Neuropsychological and neuroprotective conditions	Lu et al., 2006; Nagpal et al., 2012; Mansouri et al., 2013; Kahkeshani et al., 2019; Mori et al., 2020
Wound healing activity	Kokane et al., 2009
Cardiovascular disease	Priscilla and Prince, 2009; Bhattacharyya et al., 2013; Kahkeshani et al., 2019
Colitis	Pandurangan et al., 2015
Allergic skin	Bai et al., 2021
Rheumatoid arthritis	Bai et al., 2021
Obesity	Prasad et al., 2010; Gandhi et al., 2014; Variya et al., 2020
Metabolic diseases	Kahkeshani et al., 2019

It has been reported that gallic acid can be used for gastrointestinal, metabolic diseases and rheumatoid arthritis conditions (Kahkeshani et al., 2019; Bai et al., 2021). In case of wound healing, gallic acid in the *Mimosa pudica* plant is effective in skin disorders (Kokane et al., 2009). In cardiovascular conditions, gallic acid is effective in isoproterenol (ISO)-induced myocardial infarction in male Wistar rats, considering its protective effect on cardiac marker enzymes, troponin-T, LDH-isoenzyme pattern, lipid peroxidation products and antioxidant status. Increase in decreased glutathione levels in neuropsychological status, Gallic acid (20 mg/kg) given to rats fed a streptozotocin-stimulated high-fat diet has CNS effects such as an increase in catalase activity and a decrease in malonaldehyde levels in the brain, among other things, the hepatoprotective effect of gallic acid (Priscilla and Prince, 2009; Bhattacharyya et al., 2013; Kahkeshani et al., 2019). It has been reported in different studies that it reduces plasma insulin and plasma insulin, can increase GLUT4 translocation and glucose uptake activity in a wortmannin-sensitive manner, and significantly reduces the disease activity index and colon shortening and reduces histopathological evidence of injury (Prasad et al., 2010; Gandhi et al., 2014; Variya et al., 2020). It has been reported that gallic acid is used against colitis conditions (Pandurangan et al., 2015).

Biological activities

Bioactive compounds are secondary metabolites responsible for many biological activities. It is known that many compounds obtained from natural sources or synthetically have different biological activities (Mohammed et al., 2020). In this review, studies on the biological activities of gallic acid in the literature were compiled. The obtained results are shown in Table 2.

Table 2. Biological activities of gallic acid

Biological activities	Geographic regions	References
Antioxidant	China, South Korea, Nepal, Iran, Brazil	Li et al., 2005; Lu et al., 2006; Kim et al., 2007; Genwali et al., 2013; Asnaashari et al., 2014; Alves et al., 2016; Alavi Rafiee et al., 2018; Rahimifard et al., 2020
Antimicrobial	USA, Italy, Malaysia, Thailand, China, Canada	Chanwitheesuk et al., 2007; Sun et al., 2014; Li et al., 2015; Sarjit et al., 2015; Sorrentino et al., 2018; Rajamanickam et al., 2019
Anticancer and cytotoxicity activities	India, Malaysia, Taiwan, China, USA, South Korea	Hamada et al., 1997; Park et al., 2008; Saxena et al., 2008; Chen et al., 2009; Forester and Waterhouse, 2010; Khaledi et al., 2011; Devi et al., 2014; Subramanian et al., 2015; Hsu et al., 2016; Zhang et al., 2019
	South Korea	Kim et al., 2007
Antimelanogenic	Iran	Rahimifard et al., 2020
Anti-aging	Iran	Rahimifard et al., 2020
Antidiabetic	Iran	Rahimifard et al., 2020
Antiapoptotic	South Korea	Choi et al., 2010
Antiviral	India	Chhillar and Dhingra, 2013
Antidepressant	Taiwan	Tung et al., 2009
Antiinflammatory	Taiwan	Tung et al., 2009

Antioxidant activity

Free radicals are oxidant compounds that are produced as a result of metabolic activities (Krupodorova and Sevindik 2020). Although low levels of these compounds do not exhibit harmful effects, elevated levels can lead to serious damage. The antioxidant defense system plays a role in suppressing oxidizing compounds, such as reactive oxygen species (Bal et al., 2019; Islek et al., 2021). In cases where the antioxidant defense system is insufficient, oxidative stress occurs. Serious illnesses such as cancer, cardiovascular diseases, Alzheimer's, Parkinson's, multiple sclerosis, and neurodegenerative diseases may occur in humans as a result of oxidative stress (Selamoglu et al., 2020; Saridogan et al., 2021). Supplementation with antioxidants may reduce the incidence and effects of oxidative stress-related disorders (Eraslan et al., 2021). In this context, a compilation of literature-reported studies on the antioxidant activity of gallic acid has been presented. In a study conducted in China, the antioxidant status of gallic acid was examined using the DPPH test. As a result of the study, it was reported that the LC50 value of the DPPH test was 6.0-7.29 μM (Lu et al., 2006). In another study conducted in China, the activities of antioxidant enzymes catalase (CAT) and glutathione peroxidase (GPx) in the blood and liver of aging model induced by injection of different doses of D-gal in normal mice and accelerated aging mice of different ages were investigated. As a result of the research, it was stated that the enzyme activities in mice treated with D-gal did not change much, but the enzyme activities in the blood of 9 months old SAM decreased significantly with increasing age. When gallic acid purified from rose flowers was used to treat 9-month-old male SAM, it was reported that gallic acid did not restore CAT and GPx activities, and the amount of malondialdehyde (MDA) in the liver, brain and kidney was also reported to be significantly reduced (Li et al., 2005). In a South Korean study, the effect of gallic acid on the formation of reactive species (RS) for antioxidant status was analyzed by the reduced glutathione (GSH)/oxidized glutathione (GSSG) ratio in B16 cells. Analysis results showed that gallic acid effectively down-regulated RS generation and increased the GSH/GSSG ratio (Kim et al., 2007). In a study conducted in Nepal, the antioxidant status of gallic acid obtained from the fruit of the Terminalia chebula plant, the ethyl acetate-soluble part of the methanol extract, was investigated using the DPPH test. As a result of the study, it was reported that the extract with the highest phenolic content showed the lowest LC50 and this result created a positive correlation between radical scavenging activity and total phenolic content. (Genwali et al., 2013). In a study conducted in Iran, the anti-DPPH radical effect and anti-peroxide activity of gallic acid, methyl gallate and a-tocopherol in an oil-in-water emulsion stabilized at 55 °C with Kilka fish oil and its soy protein isolate were investigated. As a result of the study, gallic acid with the lowest hydrophobicity was reported as log P=-0.28 and the most active antiradical agent value as IC50=29.5 μM, methyl gallate IC50=38.0 μM and log P=-0.23, α-tocopherol IC50=105.3 μM and daily P has been reported to be 0.70 (Asnaashari et al., 2014). In another study conducted in Iran, the DPPH test was used. As a result of the study, it was reported that gallic acid molecules containing electron donating carboxylate anion have a significantly stronger DPPH scavenging effect than pyrogallol molecules with IC50=11.4-20.2 μM values. In the case of pancreatic islet cells (Alavi Rafiee et al., 2018). Study in Iran reported a reduction in both ROS and lipid peroxidation (LPO) levels after gallic acid treatment compared to the control group. Gallic acid treatment produced a significant increase in both Ferric reducing antioxidant power (FRAP) and thiol levels. A significant increase in FRAP levels, i.e. 106.83 vs. 56.60 mM ($p < 0.001$), was observed with the effect of gallic acid against the control groups, similarly, a significant increase in thiol levels, ie 5 versus 3 μM ($p < 0.001$), was observed in the gallic acid control groups $p< 0.001$) has been reported (Rahimifard et al., 2020). In a study conducted in Brazil, it was concluded that the ABTS test of nanoparticles containing gallic acid is high, by means of radical cation measurement. (Alves et al., 2016). As a result, it has been seen that gallic acid can be an important antioxidant source according to literature data.

Antimicrobial activity

In recent years, the increase in the number of diseases caused by microorganisms has been quite high (Sevindik, 2021). The increase in resistant microorganisms caused by unconscious drug use has limited the effects of the antimicrobial drugs used. In this context, researchers turned to the discovery of new antimicrobial drugs (Mohammed et al., 2023b; Sevindik et al., 2023b). In this review, the effects of gallic acid against microorganisms were investigated in the literature. In a study conducted in the USA, the antimicrobial status of gallic acid was investigated. As a result of the study, it was reported that chitosan films combined with 1.5 g/100 g gallic acid showed the strongest antimicrobial activity against *Escherichia coli, Salmonella typhimurium, Listeria innocua* and *Bacillus subtilis* (Sun et al., 2014). In a study conducted in Italy, *Pseudomonas putida, Pseudomonas fluorescens, Pseudomonas fragi* and *Pseudomonas* spp. Gallic acid Minimum Inhibitory Concentrations (MIC) of 2.5 mg/mL for all strains and Minimum Bactericidal Concentration (MBC) were reported to be 10 mg/mL for all strains (Sorrentino et al., 2018). A study conducted in Malaysia analyzed the MIC and MBC results of gallic acid against *Campylobacter jejuni* and *Campylobacter coli*. As a result of the study, it was reported that MIC values were 15.63–250 μg mL-1 and MBC values were 62.5-125 μg mL-1 (Sarjit et al., 2015). In a study conducted in Thailand, *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhi, Vibrio cholerae, Enterococcus faecalis, Staphylococcus aureus, Staphylococcus epidermidis, Candida albicans, Aspergillus* sp., *Fusaum Penicium* sp., and Gallic acid against *Trichophyton rubrum, Salmonella typhi* and *Staphylococcus aureus* with MIC values of 2500 and 1250 μg/mL,

respectively (Chanwitheesuk et al., 2007). In a study conducted in China, the MIC values of gallic acid against *Escherichia coli, Staphylococcus aureus* and *Candida albicans* were reported to be 6 µg/mL, 30 µg/mL and 34 µg/mL, respectively (Li et al., 2015). In a study conducted in Canada, it was reported that gallic acid was effective against *Mannheimia haemolytica* and *Pasteurella multocida* at 250 and 500 µg/mL, respectively (Rajamanickam et al., 2019).

Anticancer and cytotoxicity activities

Cancer mortality is increasing day by day. Different treatment methods are applied according to different cancer types (Sevindik, 2020). In addition, the variety of drugs used as supplements is quite large (Bal et al., 2017). In this study, the effects of gallic acid against different cell lines reported in the literature were compiled. In a study conducted in India, it was reported that gallic acid exerts 96 µg/Ml and 80 µg/Ml effects on HCT15, human colon cancer cell line and MDA MB 231, human breast cancer cell line, respectively (Devi et al., 2014). A study conducted in Malaysia showed that gallic acid and its derivatives can be used as a potent drug for cancer treatment alone as well as in combination with other anticancer drugs for the purpose of increasing the effectiveness of chemotherapy (Subramanian et al., 2015). In a Taiwanese study, gallic acid acts on DU145 prostate cancer cells through the generation of reactive oxygen species (ROS) and mitochondria-mediated apoptosis reversed by catalase and N-acetylcysteine, and by activating Chk1 and Chk2 and inhibiting Cdc25C and Cdc2 activities. It has been reported to block the growth of DU145 cells in the G2/M phases (Chen et al., 2009). In a study conducted in China, it was reported that gallic acid exerts independent anticancer effects on NSCLC A549 cells and facilitates the anticancer effects of cisplatin by modulating the JAK/STAT3 signaling pathway and downstream apoptotic molecules (Zhang et al., 2019). A study conducted in India reported that gallic acid has an IC50=2.2 µM value against MCF-7, that is, hormone-dependent breast cancer cell line (Saxena et al., 2008). In a study conducted in Japan, it was reported that gallic acid inhibited the killing activity of the CD8+ CTL clone at 30 µM (Hamada et al., 1997). In a study conducted in the USA, gallic acid was incubated with Caco-2 cells at 140 µM for 24 hours for cytotoxic status. As a result of the study, it has been reported that it inhibits cell proliferation (Forester and Waterhouse, 2010). In a study conducted in South Korea, it was reported that gallic acid inhibited the growth and proliferation of testicular cells in a dose-dependent manner and significantly increased the intracellular hydrogen peroxide level in mouse spermatogonia (Park et al., 2008). In a study conducted in Taiwan, it was reported that gallic acid caused significant cytotoxicity in DBTRG-05MG cells and this cytosolic Ca2+ was partially prevented by pre-chelating with BAPTA-AM (Hsu et al., 2016). In a study conducted in Malaysia, it was reported that gallic acid-based inadol has an effect against HCT-116 (human colon cancer cell line) and MCF-7 (estrogen-dependent human breast cancer cell line) (Khaledi et al., 2011). According to the literature data, it has been observed that gallic acid has significant anticancer activity against different cell lines.

Other activities

In the literature, it has been seen that gallic acid has different biological activities apart from its antioxidant, antimicrobial and anticancer activities. In a study conducted in South Korea, the effects of gallic acid on fungal tyrosinase, tyrosinase inhibitory activity and melanin content were investigated using B16 melanoma cells. As a result of the study, it was reported that it has a strong anti-tyrosinase activity, effectively suppresses the murine tyrosinase effect and the amount of melanin, and its LC50 value is 3.59×10^{-6} (Kim et al., 2007). In a study conducted in Iran, the anti-aging, antidiabetic and antiapoptotic status of gallic acid was examined. As a result of the study, REF cells treated with H2O2 for anti-ageing showed a significant increase in β-galactosidase concentration compared to the control group and a significant increase in G0/G1 arrest in the cell cycle group, a significant increase in basal phase insulin secretion for antidiabetic and gallic cell cycle versus control. The increase in the acid group was from 2.2 to 7.3 mU/mg protein/hr ($p<0.001$) and for the antiapoptotic status, there was a significant decrease in viable cell number compared to Acridine orange (AO) and ethidium bromide (EB) double staining. It has been reported that a decrease in necrotic cells and a decrease in caspase-3 and 9 activities were observed in flow cytometry assay (Rahimifard et al., 2020). In a Taiwanese study, gallic acid showed CCl4-induced hepatic pathological damage and significantly increased levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and malondialdehyde (MDA) and cytochrome P4502E1 (CYP2E1) protein expression and superoxide dismutase (SOD) in hepatic samples, glutathione peroxidase (GPX) and catalase (CAT) activities have been reported to decrease (Tung et al., 2009). In a study conducted in South Korea, it was reported that gallic acid actively inhibits HRV2 and -3 replications on human rhinoviruses (HRVs) from an antiviral aspect (Choi et al., 2010). In a study conducted in India, it was reported that gallic acid significantly inhibited stress-induced MAO-A activity, malondialdehyde levels and catalase activity (Chhillar and Dhingra, 2013). In this context, it has been seen according to the literature data that gallic acid has important biological activities.

Daily use and toxicity

Gallic acid (3,4,5-trihydroxybenzoic acid) and its derivatives are polyphenolic compounds found in daily diets and herbal medicines. It is also abundant in beverages such as fruits, vegetables, tea and wine. Gallic acid is easily absorbed in the gastrointestinal tract compared to other acids. Food sources of dietary polyphenols can reach up to one gram, since the average daily intake of gallic acid. It is located along the shikimate path and mainly in free form. There have been some studies of daily intake involving oral dosing such as propyl, octyl, dodecyl esters of gallic acid. When these studies are examined; 1 g/kg for Sprague-Dawley mice and 5 g/kg for Swiss albino mice for non-significant levels of side effects. Subchronically orally, in a colony with F334 is 119 mg per day for mice and 240 mg for Sprague-Dawley rats. Subacutely, it is 1 g/kg for Swiss albino rats. Oral ingestion of 5g/kg caused toxicity to rabbits. 500 mg/kg intraperitoneally induced liver damage for mice (CD-1). Gallic acid and its derivatives also have an acceptable daily intake (ADI) of 0.2 mg/kg body weight (as the sum of propyl, octyl and dodecyl gallates) (Dollahite et al., 1962; Van der Heijden et al., 1986; Rajalakshmi et al., 2001; Galati and O'brien, 2004; Jaijoy et al., 2010; Shi et al., 2013; Kosuru et al., 2018; Shree et al., 2020). Another study in the literature reported that there was no significant change in morphological and behavioral parameters in mice administered high doses of gallic acid (900 mg/kg/day) for 28 days (Variya et al., 2019). In a different study, 800 mg dose of gallic acid alone, taken directly or with spices, was administered for 8 weeks. As a result of the study, it was reported that gallic acid had no effect on weight loss or reducing food intake (Roberts et al., 2007). In different studies conducted in this context, it has been observed that gallic acid does not show any serious toxicity. In addition, toxicity studies are insufficient in the literature.

CONCLUSION

Gallic acid is one of the important secondary metabolites. In this review, the general properties of gallic acid, its pharmacological and therapeutic effects, its derivatives and biosynthesis, biological activities, daily use and toxicity are reviewed. As a result of literature research, it has been seen that gallic acid is a very important compound with many biological activities, pharmacological and therapeutic effects. In this context, the use of gallic acid in pharmacological designs is recommended. In addition, it was observed that the toxicity studies of the compound were not sufficient. There are no studies on the physiological effects of the compound in long-term use. Additionally, potential allergenicity and toxicity studies are needed to evaluate new reaction products of gallic acid and its derivatives and determine their concentrations. In addition to all these, it is obvious that gallic acid has a very high potential for use in drug designs.

Author Contributions: Conceptualization, F.S.M and M.S.; methodology, F.S.M and M.S.; validation, C.B., I.U., F.S.M and M.S.; investigation, I.U., F.S.M., A.E.Ş. and M.S.; resources, C.B., I.U., F.S.M., A.E.Ş. and M.S.; data curation, C.B., I.U., F.S.M., A.E.Ş. and M.S.; writing—original draft preparation, C.B., I.U., F.S.M., A.E.Ş. and M.S.; writing-review and editing, C.B., I.U., F.S.M and M.S. All authors have read and agreed to the published version of the manuscript.

Funding Source: No funding

Conflicts of Interest

The authors declare that they do not have any conflict of interest.

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