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A Review on Chemical Nature and Pharmacological actions of Multifunctional Osthole

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ABSTRACT-

Osthole, better known as osthol, comes from the coumarin found in Cnidiummonnieri and Angelica pubescens, among other medicinal plants.It has been reported that osthole from Cnidiummonnieri (L.) Cusson can inhibit plant pathogen.It can be extracted and separated from plants or fully integrated. Several studies have found that osthole has anti-cancer, anti-inflammatory, neuroprotective, osteogenic, cardiovascular protective, antibacterial, and antiparasitic properties. In addition, some research has been done on the efficiency and effectiveness of osthole. This article covers a comprehensive list of Osthole sources and the current state of change. It also covers the most recent biological work of osthole, which could be very helpful in future research.Osthole has been shown to have anti-inflammatory and anti-proliferative properties.Osthole inhibited cell proliferation and caused cell cycle arrest in lung and ovarian cancer.Osthole regulated phosphorylation of signaling proteinsin human breast cancer cells. Furthermore, osthole-induced activation of JNK protein-mediatedapoptosis in both cell lines.

Keyword: -Cnidiummonnieri, Breast Cancer, Osthole, Ion Channel Control, Hepatitis.

Introduction-

Osthole (also known as osthol) is a natural coumarin found in the Cnidium plant. 7-methoxy-8- (3-methyl-2-butenyl) -2H-1-benzopyran-2-one. The ripe fruit Cnidiummonnieri (FructusCnidii), commonly used in Traditional Chinese Medicine (TCM) clinics, contains high levels of osthole, as do other medicinal plants such as Angelica, Archangelica, Citrus, and Clausena. Most of the therapeutic effects of FructusCnidii are considered to be one of its most important bioactive compounds, osthole [1, 2], which stimulates the immune system and improves male function while reducing rheumatic pain and removing moisture. Antioxidant, anticancer, anti-inflammatory, and immunomodulatory functions of osthole have been found in recent studies [1, 3, 4]. The development of osthole and the emergence of alternatives as a targeted treatment should be encouraged, given the various activities of osthole described. As a result, it is important to examine the medical and biological studies of this coumarin, as well as the basic mechanisms of its action and the full picture of its various roles. Osthole has a wide variety of biological and pharmacological effects. Although the effects of osthole are divided into different biological processes in this study, there is a strong correlation between them (Figure 1).

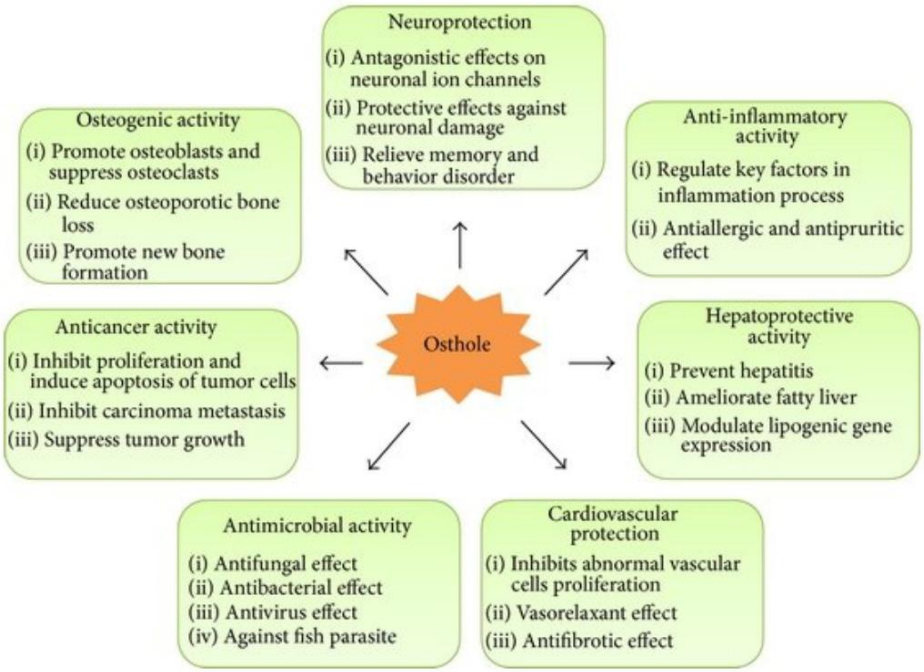


Fig.1- Several systemic pharmacological and therapeutic effects, as well as related experimental findings

7-methoxy-8- (3-methyl-2-butenyl) -2H-1-benzopyran-2-one, commonly known as osthol, is a natural coumarin isolated from the Cnidium plant. The small fruit Cnidiummonnieri (FructusCnidii), widely used in traditional Chinese medicine, contains high levels of osthole [5, 6]. Angelica, Archangelica, citrus, and Clausena are a few medicinal plants that contain osthole. Osthole shows anti-inflammatory, anticancer, antiapoptosis, antithrombosis, and anti-aggregation properties [7]. Several studies have shown that osthole has a hepatoprotective effect. Osthole has been shown to reduce the release of hepatitis B virus (HBV) from cell culture and to protect mice against concatitis caused by concanavalin A or the anti-Fas antibody [8,9,10]. Osthole promotes hepatic fibrosis, inhibits hepatic stellate cell function [10], enhances antitumor immune responses [12,13,14], and reduces the development of hepatocellular carcinoma [15]. It also slows the growth of hepatocellular carcinoma. In the mouse model of bleeding caused by trauma, osthole also protects against liver damage [16]. Osthole, as shown in a recent study, is an effective treatment for acetaminophen liver injury (APAP) [17], a condition characterized by oxidative stress [18]. On the other hand, the effect of osthole on hepatotoxicity induced by TMX was not studied. In this work, we examined the effect of osthole on TMX caused by severe liver damage and the underlying mechanism.

Pharmacokinetics and Metabolism of Osthole -

The pharmacokinetics of osthole in mouse plasma after oral or intravenous treatment were investigated using the HPLC method, which produced a concentration / time curve with a rapid distribution phase followed by a long term phase [19 - 22]. Ozone absorption in the rat single pass intestine perfusion (SPIP) model was investigated using HPLC, and the results revealed that osthole absorption was a diffusion process performed in all parts of the intestine [23]. In male SD mice, osthole metabolism was assessed following oral administration, and 10 phase I and 3 phase II metabolites were excreted and detected in urine. Hydroxylation, demethylation, and hydrogenation were the most important phases of metabolic I, while glucuronidation contributed to phase II metabolism [24]. In the human colorectal Caco2 cell model, osthole absorption and metabolism were also examined. Desmethyl-osthol and its various isomers have been an important phase I metabolite for Caco-2 cells, which have a strong penetration and accumulation [25,26]. CAMP and cGMP levels .In a study of osthole biological functions, it was found that osthole induces indirect proliferation of intracellular and tissue cAMP and cGMP, which may be involved in the basic mechanism of some of the osthole organisms. The second messengers, cAMP and cGMP, produced at ATP and GTP, respectively, are important in many biological processes. CAMP significantly affects protein kinase A (PKA), as well as ion channels and growth hormone, by activating it. CGMP regulates ion channels involved in cell cycle binding, apoptosis, and smooth muscle relaxation. Osthole increases cAMP and cGMP levels by inhibiting phosphodiesterases (PDEs), which in turn hydrolyzecAMP and cGMP by destroying the phosphodiester link [27,28] .Increased cAMP and cGMP

-osthole was found to be associated with an action to prevent vascular smoothness. muscle cells [29] .when cGMP / PKG-dependent pathway stimulation was linked to the release of osthole-induced glutamate into the hippocampus synaptosomes [30]. Increases in cGMP have been found to be responsible for the inhibition of osthole-mediated inflammatory substances in the carrageenan model [31]. In addition, the researchers speculated that the osorelaxantosthole properties were linked to higher levels of cAMP and cGMP as a result of osthole treatment [32, 28, 33]. (Figure 1).

Ion Channel Regulator-

In many cells and tissues, osthole has been reported to alter membrane and other ion channels, including sodium channels, acidsensing ion channels, CFTR chloride channels, and especially calcium channels. The action of osthole in these ion channels is linked to osthole bioactivities, which include vasorelaxant, immunomodulatory, and antifibrotic effect, as well as its neuronal and neuroendocrine activities, which include neuroprotective, anticonvulsant, and pain relievers. Calcium depletion, on the other hand, affects the activity of osteoprogenitors, which play an important role in both bone homeostasis and regeneration [34,35], making the calcium channel a promising way to investigate the mechanism of osteogenic osthole effect. CAMP and cGMP have long been known to play a role in regulating L-type Ca2 + channels and other ion channels [36, 37, 38]. As a result, mutations in cAMP and cGMP levels are at least a major cause of the osthole effect on ion channels (Figure 2).

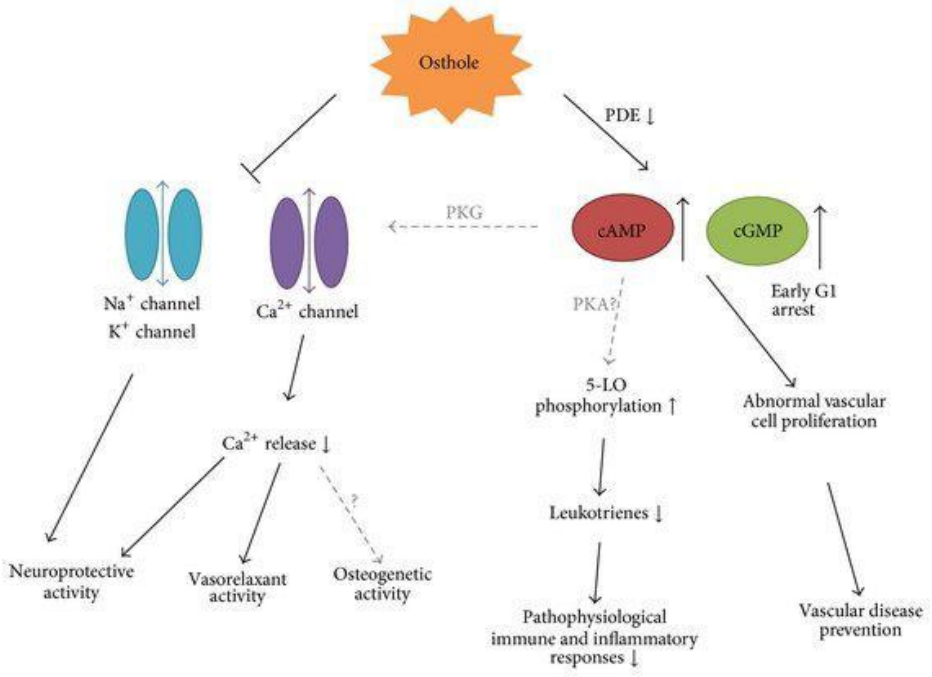
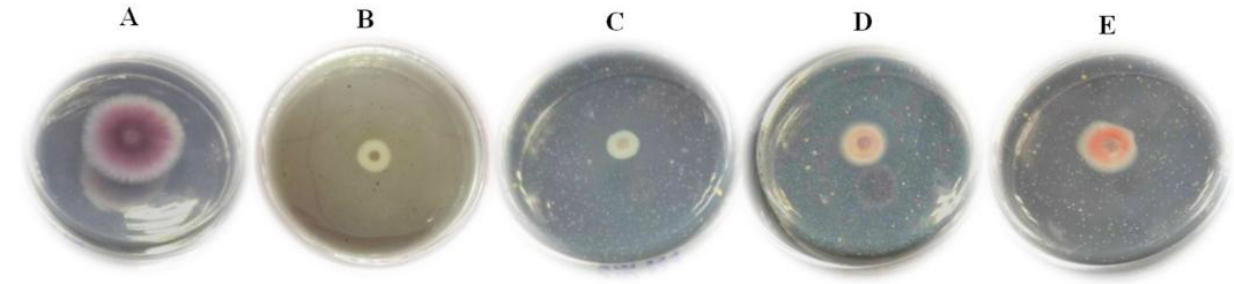


Fig.2.Possible connections between osthole's influence on intracellular ion channels, cyclic adenosine monophosphate (cAMP) levels, and cyclic guanosine monophosphate (cGMP) levels, as well as some of their pharmacological action. (A dashed line indicates unconfirmed possibilities in osthole research.)

Osthole (7-methoxy-8-isopentenoxycoumarin) is a monomer isolated from cnidiummonnieri (L.) Cusson that exhibits anti-inflammatory, anti-inflammatory, and leishmanial properties (39,40). Traditional Chinese medicine has been used to treat a variety of ailments, including allergies, inflammation, HIV infection, and diabetes, in clinics for many years. In several types of human cancer, osthole has been shown to have anti-inflammatory and anti-proliferative properties. Osthole, in particular, promotes tumor cell death, inhibits cell cycle development, and inhibits tumor cell migration (41-48). In addition, osthole has been shown to enhance the anticancer activity of cisplatin in rhabdomyosarcoma cells (49) and to prevent hepatocellular carcinoma in other studies (46). These findings suggest that osthole may play a role in the treatment of human cancer, particularly cervical cancer. In this study, the anticancer activity of osthole was tested in vitro as a single agent or in combination with irradiation. In cervical cancer cells, the basic cellular events of osthole treatment were also considered. This should have been the first step in determining whether osthole should be used to treat cervical cancer. Recent research suggests that osthole is a potent antidepressant for many diseases of the nervous system and effectively crosses the blood-brain barrier. Oral osthole treatment reduces the inflammatory response to local

ischemic stroke [50], whereas intraperitoneal injection has a neuroprotective effect on traumatic brain injury due to its antioxidative and antiapoptotic properties [51]. In transient cerebral ischemia, osthole treatment enhances neurobehavioral function and reduces infarct volume [52]. In addition, osthole has been shown to protect against acute ischemic stroke caused by middle cerebral ischemia when administered intraperitoneally. Potato Fusarium wilt is a common soil-borne disease that causes severe symptoms of rot and ultimately plant death, which has a direct impact on potato harvesting and quality [54,55,56]. The disease is widespread worldwide, and often results in a 30% loss of productivity. According to Rakhimov et al. (2000), potato Fusarium wilt is caused by one of the five species of Fusarium: FusariumoxysporumSchlecht, Fusariumsolani (Mart.) Sacc., FusariummoniliformeSheld, FusariumsambucinumFuckel, and Fusariumnivale (Fr.) Ces. F. oxysporumSchlecht, F. sol (Fr.)

In Inner Mongolia, China, Ces are agents of potato Fusarium wilt. Because the disease is a soil-borne pathogen-resistant strain, chemical treatment of soil in the field is a challenge [57]. In the fight against potato Fusarium wilt, contamination and persistence of fungicide residues in potato stages are major challenges. On the other hand, fungicides derived from plants, are attractive options because they are not phytotoxic, easily biodegradable, and environmentally safe [58]. Proteins, alkaloids, flavonoids, phenols, essential oils, and polysaccharides are examples of plant components that have antifungal effects [58 - 63]. Cnidiummonnieri (L.) is a traditional Chinese plant found throughout China [64 - 62]. C. monnieri contains a total of 429 chemicals, 56 of which were chemically identified [67]. Osthole is an O methylated coumarin that was obtained and purified from C-seeds. monnieri. It has been shown to have pharmacological properties in humans, including anti-allergic, anti-pruritic, anti-bacterial, anti-dermatophytic, anti-osteoporotic, and anti-fungal effects [68 - 72]. In addition, osthole has been shown to promote osteogenesis in osteoblasts by regulating transcription factor osterix by cAMP / CREB signaling [73].



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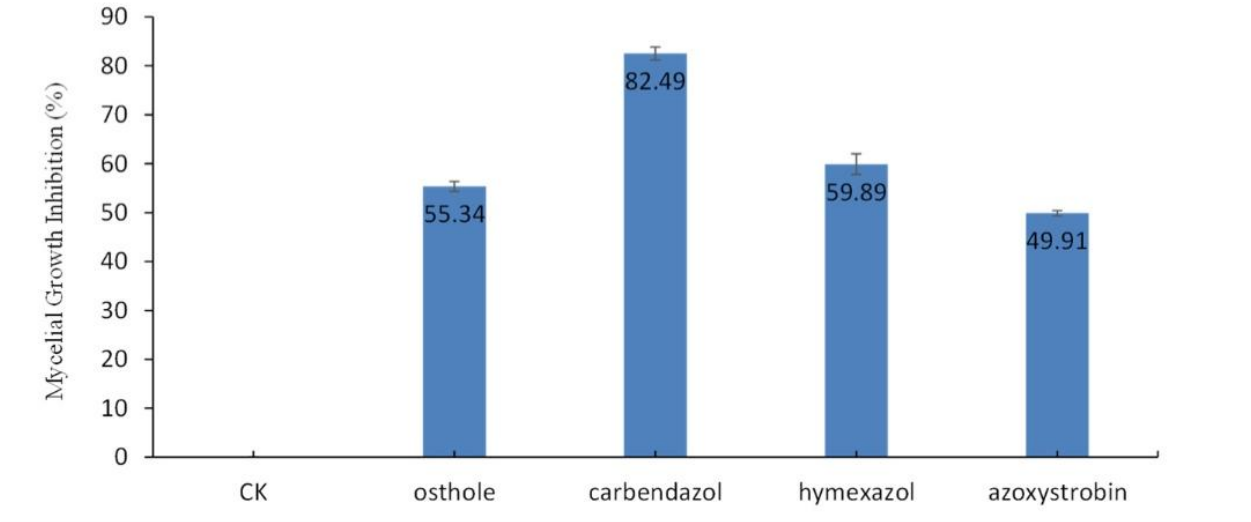

Fig. 3: 3 days after injection, osthole has a preventive effect on Fusariumoxysporum. (A) CK, potato dextrose agar (PDA) medium; (B) PDA medium plus 5 mg / mL osthole; (C) PDA medium plus 5 mg / mL carbendazol powder wettable; (D) PDA medium plus 5 mg / mL hymexazol aqueous solution; (E) PDA medium plus 5 mg / mL azoxystrobin; (F) In PDA medium, CK The normal deviation is indicated by the bars in the columns.

In the United States, breast cancer is the leading cause of death by cancer [74]. The incidence of breast cancer has been steadily increasing and it is predicted that it will continue [75]. The pathogenesis of breast cancer is accelerated by altering reproductive patterns, such as pregnancy in later years and shorter breastfeeding [76]. Because fewer symptoms appear in the early stages of breast cancer, it is more commonly found in the advanced stages. Although diagnostic and therapeutic approaches have improved, many barriers to treatment persist, including metastasis, adverse pharmacological effects, and drug resistance [77]. About 50% of patients with advanced breast cancer are resistant to radiation due to the hypoxic tumor nature [78]. In addition, the heterogeneity of breast cancer makes it difficult to treat with certain chemotherapeutic drugs [79]. Based on gene expression profiles, breast cancer cells can be divided into five subtypes: luminal A, luminal B, HER2-overexpression, basal, and normal similarities. Clinical outcomes vary depending on the subtype [80].

Coumarin and its derivatives have been extensively investigated in terms of their biological effects. The molecular structure of coumarin is thought to play a role in its pharmacological activities [81]. Coumarin extracts have been used to treat CNS infections as well as anticoagulants and anti-HIV drugs [82,83,84].

Osthole (7-methoxy-8- (3-methyl-2-butenyl) coumarin) is a phytochemical found in Cnidiummonnieri (L.) Cusson, a plant of traditional medicine. Osthole is an anti-inflammatory, antimicrobial, and anti-allergic [85,86]. It has received many reports for its anti-cancer properties. Osthole has been shown to be effective in treating cancers such as lung, liver, cervical and ovary cancers.

Osthole also induced apoptosis in immature hepatocellular carcinoma cells and prevented the formation of hepatic tissue in mice [87]. Osthole inhibited cell proliferation and caused cell cycle arrest in lung and ovarian cancer [88,89] .It inhibits cell growth and metastasis, which has anti-cancer properties in breast cancer [90]. According to a recent study [91], Osthole blocked triple-negative breast cancer cell lines by blocking the STAT3 signaling pathway. Reduces cell proliferation and stops cell cycle. Osthole weakens the mitochondrial membrane and increases the levels of cytosolic calcium, which disrupts cellular homeostasis. In addition, osthole induced apoptosis in breast cancer cells by activating ER stress proteins and regulating the activity of PI3K / Akt and MAPK signaling pathways (Figure 4).

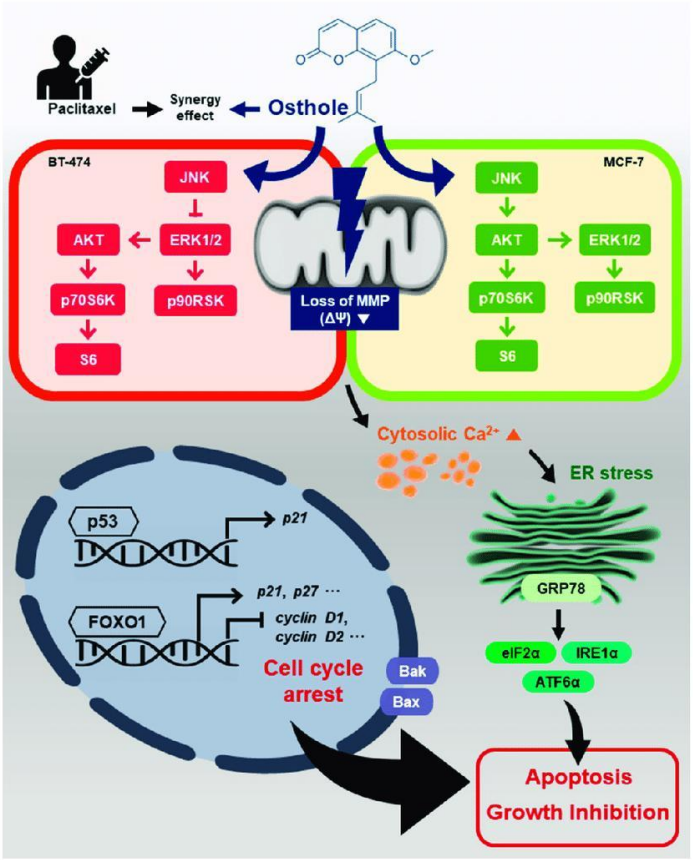

Figure 4 shows a possible osthole mechanism in human breast cancer cell lines. Osthole resulted in the loss of MMP and an increase in cytoplasmic calcium levels. In BT-474 and MCF-7 cells, protein-response proteins and pro-apoptotic proteins are increased. Osthole inhibited JNK in both cell lines, reduced the hallmark modes of Akt and ERK1 / 2 in BT-474 cells, and inhibited these pathways in MCF-7 cells. In breast cancer cells, Osthole caused growth inhibition and apoptosis.

We also looked at osthole (7-methoxy-8- (3-methyl-2-butenyl) -2H-1-benzopyran-2-one), C prenylatedcoumarin derivative and neuroprotective, osteogenic, anticancer, hepatoprotective, and possible antioxidant. results (fig.5). The leaves of citrus [92] and Cnidiummonnieri, a flowering plant used in traditional Chinese medicine, contain osthole. For centuries, C. monnieri is used to treat itching, irritation, and other skin conditions [93].

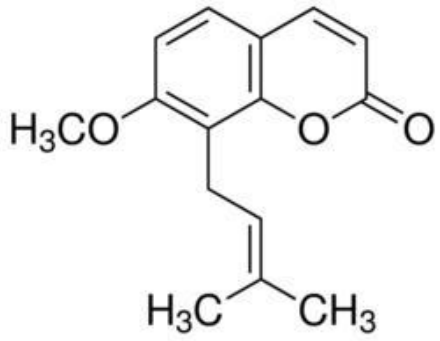

Fig.5 Chemical structure of osthole

Table 1. X-ray Crystal Structural Characterization of Osthole

Name	Osthole
Empirical Formula	$C_{15}H_{16}O_3$
Formula Weight	244.28
Crystal System	Triclinic
Space Group	P-1
Unit Cell Dimensions	7.4543(11) Å 65.145(3)° 9.4107(14) Å 74.836(3)° 10.7594(16) Å 70.553(3)°
Volume	639.23(17) $Å^3$
Z	2
Absorption Coefficient	0.088 mm^{-1}
Crystal size	0.280 × 0.190 × 0.050 mm^3
Θ range data collection	2.107 to 32.054°
Reflections Collected	16,847
Independent Reflections	4224 [R(int) = 0.0273]
Completeness to Θ = 25.242°	100.0%
Absorption correction	Empirical
Data/restraints/parameters	4224/0/228
Goodness of fit on F^2	1.034
Final R indices [I > 2 σ(I)]	R1 = 0.0425, wR2 = 0.1169
R indices (all data)	R1 = 0.0560, wR2 = 0.1276
Largest diff peak and hole	0.417 and −0.248 e.$Å^{-3}$

X-ray ostholedata.All data collected at temperature = 125 (2) k and (Mo) lambda = 0.71073 Angstrom. The structure of the osthole has already been defined at room temperature [94] .The boundaries of our cell and the structure of 1989 (CCDC code JAKFIK) are related to our reduced cell. (Tble 1 summarizes our osthole crystal structure data). Figure 6, shows the formation of osthole cells, which do not produce unique features. As shown in Figure 5, the crystal structure shows intermolecular and osthole interactions with offset coagulation pattern.Figure shows how the molecule is folded into C10, at an angle of 74 ° between the aromatic coumarin system and the alkyl component. Offset stacking is similar to bergamottin, but with CH ... O (carbonyl) hydrogen bond 3.576 (3) and CHO angle 161 (1) instead of 3.366 and CH. .. O weak (carbonyl) hydrogen bond of 3.576 (3).

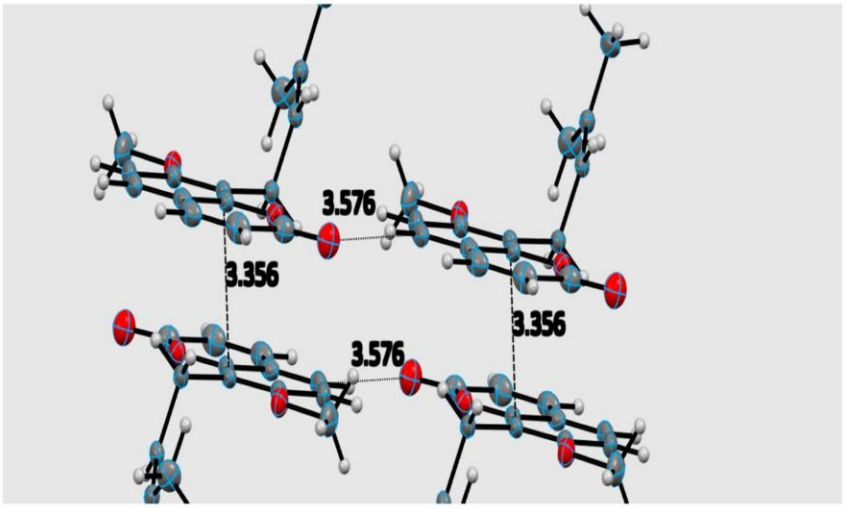

fig.6 Hydrogen interaction and accumulation of osthole crystal structure

conclusion-

Numerous studies have shown that osthole has therapeutic benefits such as neuroprotection, osteogenesis, immunomodulation, and anti-cancer properties, making it an additional multitarget drug and effective diet. Although the basic mechanisms of these characteristics are unknown, the action of osthole control at cAMP and cGMP levels, as well as specific ion channels, can be considered as a contribution to their value. Further research is needed to improve our understanding of the effects of osthole medication and to address safety concerns in order to use this natural substance and its extracts as a preventive and curative agent in humans. In human breast cancer cells, we have found that osthole has anti-cancer properties. Osthole reduced cell growth by lowering the levels of PCNA and caused cell cycle arrest. Collectively, these findings suggest that osthole may have significant therapeutic promise in glioma patients. Further research is needed to determine the exact effect that osthole has on cervical cancer. We also found that osthole has an anti-tumor effect on TNBC cells, as well as mechanisms that may support it.

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