# Biological Effects Of Licochalcones

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**BIOLOGICAL EFFECTS OF LICOCHALCONES**

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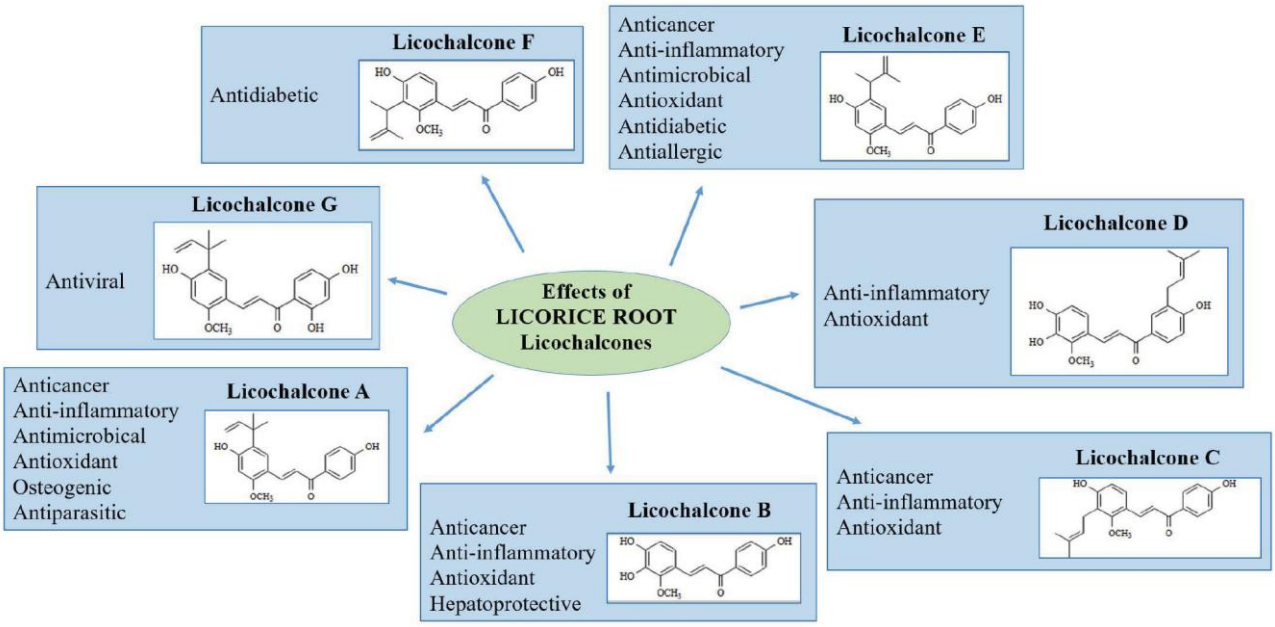
**Abstract**

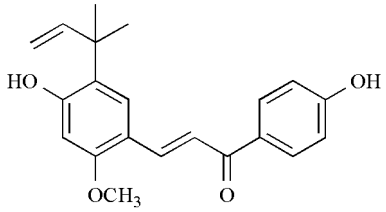
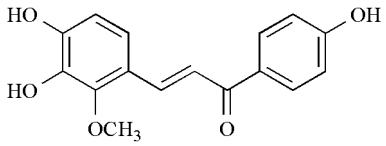
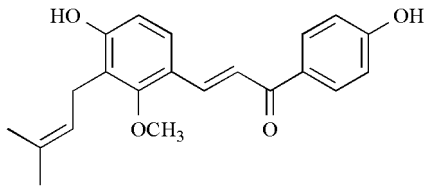
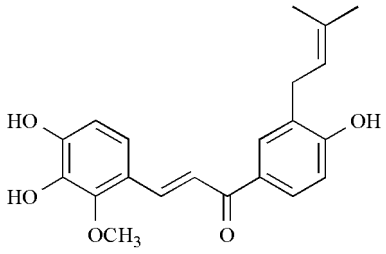
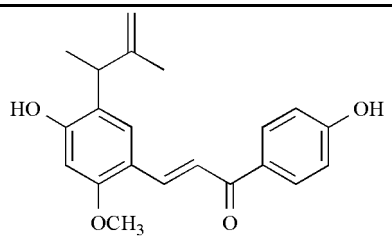
Medicinal plants and their natural bioactive molecules, are evaluated as the foundation for health preservation and care of humanity. The licorice root, known as "*Radix Glycyrrhizae*", is a perennial plant that comes from Mediterranean countries, central to southern Russia, Asia, Turkey, Iraq and Iran. The licorice root has been used in traditional Chinese medicines for centuries and has been defined as "*the progenitor of herbs*". The name 'Licorice' derive from the ancient Greek word *Glukurrhiza*, meaning 'sweet root'. It consists of approximately 30 species, however the most common ones consist of *Glycyrrhiza glabra L., Glycyrrhiza uralensis Fisch* and *Glycyrrhiza Inflata.* In addition, the licorice root contains chalcones, which are part of an important class of natural products and are precursors of flavonoids. Chemically, chalcones are formed of two aromatic rings associated with α, β-unsaturated α-carbon ketone, representing the prima nucleus of the structure. They have been classified, according to chemical structures, in Licochalcone A, B, C, D, E, F and G. This review aims to highlight all the *in vitro* and *in vivo* studies that have been conducted on the licochalcones, extracted from *Glycyrrhiza species.* The main effects are as follows: anti-inflammatory, antioxidant, anticancer, antimicrobial, antiviral, antiallergic, antidiabetic, hepatotoxic and osteogenic. It is important to implement the introduction of biologically active natural molecules from the bench (research) to the bedside (clinical practice). However, when looking at the future, it is required to perform additional studies to validate these biological effects.

**Keywords: Licocalchones, *Glycyrrhiza species*, biological effects, anti-inflammatory, antioxidant, natural compounds.**




## 1. INTRODUCTION

Medicinal plants and their natural bioactive molecules, are evaluated as the foundation for health preservation and care of humanity [1, 2].Even though, several evidences show the (pre)clinical performance and security of multi-target natural products, they are still underestimated as initial points for multi-target drug discovery [3].The licorice root, known as "*Radix Glycyrrhizae*", is a perennial plant that comes from Mediterranean countries, central to southern Russia, Asia, Turkey, Iraq and Iran. The licorice root has been used in traditional Chinese medicines for centuries and has also been defined as "*the progenitor of herbs*"[4]. The name 'Licorice' derive from the ancient Greek word *Glukurrhiza*, meaning 'sweet root' [5]. It consists of about 30 species. Licorice sources, which are used in tobacco, foods, cosmetics, and in both herbal and traditional medicine, are known as *Glycyrrhiza glabra L.*, *Glycyrrhiza uralensis Fisch* and *Glycyrrhiza Inflata* [6]. The pharmacological efficacy of the components of licorice in pathologies such as atherosclerosis, cancer, bacterial infections, gastric ulcer has been demonstrated [7-11]. Pharmacologically, licorice extracts have been used as a remedy for gastric ulcer and for anti-allergic and antihistaminic preparation. The phytochemical *Glycyrrhiza* root extract contains triterpenoid saponins, flavonoids, isoflavones, coumarins, stilbenoids and miscellaneous compounds [12]. In addition, the licorice root contains chalcones, which are part of an important class of natural products and are precursors of flavonoids. Chemically, chalcones are formed of two aromatic rings associated with α, β-unsaturated α-carbon ketone, representing the main nucleus of the structure. Therapeutic uses of chalcones trace back thousands of years through the employ of plants and herbs for the treatment of several medical disorders [13].They are classified according to chemical structures in Licochalcones (Lico) A, B, C, D, E, F and G (Table 1). Several *in vitro* and *in vivo* studies have evidenced beneficial properties of these bioactive components such as anti-inflammatory, antimicrobial, antiviral, antioxidant, antihepatotoxic, anticancer, osteogenic, antidiabetic and antiallergic activities (Table 1) [14]. Emerging research have been highlight the medicinal significance of licorice and have previously been reported in the literature, while in this review article, evidence is given on diverse biological activities of licochalcones, licorice's metabolites, published in the last twelve years (2005–2017).

| **Compounds** | **Structure** | **Source** | **Effects** |
|---|---|---|---|
| *Licochalcone A* |  | *Glycyrrhiza species* | ***Anticancer [62,64,66,68]*** ***Anti-inflammatory [25,27]*** ***Antimicrobical [84,88]*** ***Antioxidant [44]*** ***Osteogenic [97]*** ***Antiparasitic [93,95]*** |
| *Licochalcone B* |  | *Glycyrrhiza species* *New synthesis* | ***Hepatoprotective [99]*** ***Anticancer [70]*** ***Anti-inflammatory [28,29]*** ***Antioxidant [53]*** |
| *Licochalcone C* |  | *Glycyrrhiza species* | ***Anti-inflammatory [30,37]*** ***Antioxidant [51]*** ***Anticancer [75]*** |
| *Licochalcone D* |  | *Glycyrrhiza species* | ***Antioxidant [54]*** ***Anti-inflammatory [39]*** |
| *Licochalcone E* |  | *Glycyrrhiza species* | ***Anticancer [71]*** ***Anti-inflammatory [40]*** ***Antimicrobical [85]*** ***Antioxidant [55]*** ***Antidiabetic [102]*** ***Antiallergic [107]*** |

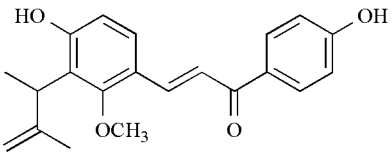
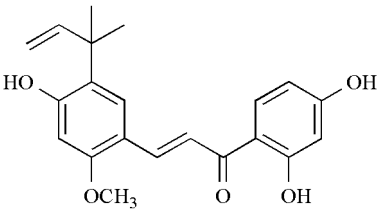
| | | | |
|---|---|---|---|
| *Licochalcone F* |  | *Glycyrrhiza species* | ***Antidiabetic [103]*** |
| *Licochalcone G* |  | *Glycyrrhiza species* | ***Antiviral [90]*** |

**Table 1.** Summary of licochalcones identified in licorice extracts, their potential effects on various diseases in several *in vitro* and *in vivo* studies.

## 2. ANTI-INFLAMMATORY ACTIVITY OF LICOCHALCONES

Inflammation is a complex cellular defense mechanism mediated by an imbalance between several immune and inflammatory cells. Inflammatory reactions are often a set of processes involving the overproduction of proinflammatory mediators such as IL-6, IL-17, IL-1β, tumor necrosis factor (TNF) -α, prostaglandin E2 (PGE2), nitric oxide (NO) and Regulated on Activation Normal T Cell Expressed and Secreted [15-17]. Most of our knowledge of signaling in inflammation is gained from downstream signal transduction regulators such as nuclear factor κappa B (NF-κB), the mitogen-activated protein kinase (MAPK) family like p38 MAPK, NH2-terminal kinase c-Jun (JNK) and extracellular-regulated kinase (ERK) as well as activator protein 1 (AP-1) [18, 19]. Several stimuli, such as lipopolysaccharides (LPS), cytokines, prooxidants molecules, activators of protein kinase C, trigger NF-κB via phosphorylation of Inhibitor κB. This leads to rapid nuclear translocation of the NF-κB, whit consequently activation of the transcription of target genes, including genes encoding for proinflammatory protein and inducible enzymes like cyclooxygenase 2 (COX-2) and inducible nitric oxide synthase (iNOS) [20, 21]. Since NF-κB, MAPK and AP-1 have played a major role in the amplification inflammatory response, they are a "keystone" for acute inflammation through the use of drug inhibitors. In the last few years, the identification of bioactive natural occurring compounds with anti-inflammatory properties and the analysis of biological mechanisms have shown to decrease the incidence and severity of flogosis, thus lowering the risk of various inflammation-related illnesses [22-24]. Several studies have shown that the majority of Licochalcones strongly hinder LPS-induced NF-kB transcriptional activation by blocking the phosphorylation of NF-kB. It has been discovered that Lico A showed potent anti-inflammatory effects both *in vitro* that *in vivo* models. Lico A is able to strongly down-regulate proinflammatory cytochines levels, such as TNF-α, IL-6, and IL-1β, in RAW 264.7 cells (Myelomonocytic Murine Leukemia), in mice with acute lung injury, in serum and kidney tissues by suppression of NF-κB activation and p38/ERK MAPK signaling in a dose-dependent manner [25, 26]. Recently, has been reported that Lico A cause the potent inhibitory effect on collagen-induced platelet aggregation by inhibiting Cyclooxygenase-1 isoforms in healthy male rabbits and healthy human volunteers. Further studies should be performed to prove the mechanism of inhibition of COX-2 by Lico A as well as find another potential inhibition mechanism by other platelet activators including thromboxane $A_2$ [27]. Previously, experimental data have suggested that Lico B inhibited LPS-induced activation of Protein Kinase A and consequently reduced the LPS-induced

production of NO, TNF-α and Monocyte Chemoattractant Protein-1 [28]. Following, has been evaluated that a novel compound derivate by Lico B, (*E*)-3-(3,4-dihydroxy-2-methoxyphenyl)-1-(2,4-dihydroxyphenyl)prop-2-en-1-one (DDP), may be a potential target for treatment of various inflammatory diseases by inhibiting inflammatory reactions in macrophages and protecting mice from endotoxin shock. *In vitro* experiments have shown that DDP treatment suppresses the production of NO and pro-inflammatory cytokines, inhibiting the activation of NF-kB and AP-1 and simultaneously blocking upstream inflammatory signaling cascades. In animal model, DDP protected BALB/c mice from LPS-induced endotoxin shock, possibly through the inhibition of the production of inflammatory cytokines [29]. In 2011, has been demonstrated the potential anti-inflammatory effects of Lico C, extracted on dried roots from *Glycyrrhiza Glabra*, on THP-1 (Human Myelomonocytic Leukaemia) cells with pro-inflammatory stimuli. The capability of Lico C to reduce superoxide radical has been linked to a downregulation of iNOS *via* NF-kB inhibition and a modulation of antioxidant network activity of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx). Moreover, Lico C prevents the formation of peroxynitrite and keeps formation of 3-nitrotyrosine [30]. NO and NF-kB are important proinflammatory molecules involved in the development of several radical species during oxidative reactions [31]. Overproduction of NO by iNOS has been mainly studied in macrophages during inflammation and infection related to host defense. It has also been involved in various pathological processes, including tissue injury and cell apoptosis following inflammation and ischemia, rheumatoid arthritis, and onset of colitis [32, 33]. Thus, the scavenging activity of Lico C may perform a new pharmacological activity against inflammatory diseases which have been linked to the imbalance of the redox state. In a following study, has been highlighted the role of Lico C in the inflammatory response of septic myocardial dysfunction. Sepsis, is characterized by a systemic inflammation, which carry out to multiorgan failure with immune disorder. Septic cardiac dysfunction, caused by bacterial endotoxin LPS, is a major cause of death in patients with sepsis [21, 34]. Several studies have shown that in the vascular system, the key determinant of muscle tone is the release of NO from endothelial cells via NOS in the presence of calmodulin and $Ca^{2+}$ [35, 36]. Moreover, emerging research suggests that improvement of cardiac dysfunction in sepsis could improve the outcomes of patients. Based on these evidences, treatments for sepsis with anti-inflammatory and antioxidant drugs have demonstrated a decreased risk of cardiovascular complications [31]. Has been demonstrated that LicoC positively modulates the functional recovery and integrity of endothelial function. The results have revealed that LicoC treatment put down translocation of NF-kB and several downstream molecules, such as iNOS, Intercellular Adhesion Molecule-1 (ICAM-1) and Vascular Cell Adhesion Molecule-1 (VCAM-1). Moreover, LicoC has increased the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/endothelial nitric oxide synthase (eNOS) signaling pathway [37, 38]. These discoveries indicate that LicoC may play a pharmacological role in cardiac dysfunction in sepsis-liked inflammation. Therefore, LicoC may be employed as an adjuvant treatment in order to reduce cardiomyocyte inflammation. The scientific evidences points out that Lico D check the degranulation in RBL (Rat Basophilic Leukemia)- 2H3 cells through the block of extracellular $Ca^{2+}$ influx and phosphorylation of the MEK-ERK pathway, which is well-known to monitor cytokine production in mast cells [39]. In 2013, it has been shown that LicoE, a new retrochalcone extracted from *Glycyrrhiza inflata*, exhibits strong anti-inflammatory effects *in vitro* and *in vivo* studies. Indeed, Lico E block NF-κB and AP-1 transcriptional activity via inhibition of AKT and MAPK, implying to decrease in the expression of pro-inflammatory cytokines and of the inducible enzymes iNOS and COX-2 in mouse ear edema and LPS-stimulated RAW 264.7 [40].

## 3. ANTIOXIDANT ACTIVITY OF LICOCALCHONES

Oxidative stress is at the basis of several diseases, which is linked to complex interactions. Therefore, the mechanism that is directly implicated in controlling oxidative stress could be an attractive strategy to prevent the onset and/or hinder the progression of several diseases. The transcription factor nuclear factor-E2-related factor-2 (Nrf2) is the guardian of redox balance by regulating of antioxidant and phase II detoxification genes, which are most important to defense against oxidative stress and inflammatory responses. In physiological conditions, reactive oxygen species (ROS) concentration can be reduced by enzymatic and non-enzymatic antioxidant network systems, including antioxidant enzymes such as SOD, CAT and GPx and antioxidant molecules such as reduced Glutathione (GSH) [18, 41, 42].

Regulation of redox state plays a key role in cell viability, activation, proliferation, and organ function and is maintained by prevention and repair of intracellular molecules involved in the maintenance of equilibrate balance between oxidative and reduced species [42, 43]. In the ongoing scientific research of new safe and effective drugs, there has recently been a rediscovery of natural substances as a potential source for antioxidant therapeutic solutions for human health. Among these, in recent years, considerable interest has been directed at flavonoid [34]. Experimental investigations that Lico A protected from oxidative stress by activating the expression of cytoprotective phase II enzymes. Studies on primary human fibroblasts show that LicoA induce nuclear translocation of Nrf2 and increase the expression of the cytoprotective and anti-inflammatory enzymes, such as heme oxygenase 1 (HO-1) and glutamate–cysteine ligase modifier subunit. Lico A -treated cells expressed a higher Reduced/Oxidized glutathione (GSH/GSSG) ratio and reduced concentrations of ROS in UVA-irradiated human dermal fibroblasts just as in activated neutrophils. *In vivo* experimental studies, showed that ultraweak photon emission analysis of skin treated with licorice extract, which has high concentration of Lico A, showed a reduce UVA-induced luminescence. These findings show that topical application of licorice extract is a useful approach to enhance Nrf2-dependent protective effect in human skin [44]. Furthermore, several studies demonstrate that oxidative stress can trigger oxidative stress can trigger myocardial damage after ischemia/riperfusion (I/R) via several pathways [45]. It has also been shown that the increased concentration of heavy metals in the environment, such as vanadium, and therefore the constant exposure to massive doses of these elements could contributes modify homeostasis cardiovascular via change on of kallikrein-kinin and renin-angiotensin systems [46]. During reperfusion following ischemia, myocardial cell mitochondria and xanthine oxidase pathways overproduce ROS [47]. The mechanism involved of ROS-induced myocardial damage is as follows: ROS attack membrane phospholipids and alter the fluidity and permeability of the membrane; in this context, malondialdehyde (MDA) is produced by lipid peroxidation; myocardial enzymes, such as troponins, are produced; structural proteins and cell structures are destroyed [48, 49]. ROS-induced damage can carry to apoptosis and necrosis in cardiomyocytes. Several natural compounds are effective biological antioxidants that may slow down the development of cardiovascular disease by participating in the regulation of local vascular redox balance [50]. In 2015, experimental analysis have demonstrated the beneficial effects of treatment of Lico C on cardiac function. Certainly, they studied the potential function of Lico C in an isolated rat heart model of I/R, through modulation of myocardial enzymes, inflammatory factors, cell morphology, mitochondrial injury, and cardiomyocytes apoptosis. Moreover, they suggested that Lico C improves the recovery of cardiac function, decreases intracellular ROS formation, morphological alteration, and hinder mitochondrial damage and I/R induced cardiomyocytes apoptosis. In this experimental study, SOD activity and GSH/GSSG ratio considerably enhanced, whereas MDA level significantly reduced in the experimental group treated with Lico C. Furthermore, Perfusate Creatine Kinase (CK) and Lactate Dehydrogenase (LDH) levels, myocardical enzymes, after the treatment of Lico C significantly decreased [51]. These findings are of particular relevance considering that these enzymes are an important index of myocardial structural damage [52]. Moreover, this study proved that the treatment with Lico C reduced TNF- α levels and mitigated the histological

changes, suggesting that Lico C act as the antagonist of TNF-α. Finally, Lico C treatment enhanced the cardiac function by decreased the apoptotic index of rats after I/R, and reduced mitochondrial damage [51]. This evidence suggests that Lico C may have a potential therapeutic role for the prevention of myocardial I/R injury thanks to its antioxidant, anti-inflammatory and anti-apoptotic activities [30,51]. In 2014, experimental investigations have emphasized that Lico B has exhibited significant cardioprotective effects during I/R injury, in mice, via increasing the capacity of antioxygen free radical and anti-inflammatory agent. Indeed, MDA, LDH and CK level significantly decreased,whereas SOD activity and GSH/GSSG ratio significantly increased in the experimental group pretreated with 1 $\mu$g/mL Lico B compared with the I/R control group. Lastly, cardioprotective effects, linked to antioxidant and anti-inflammatory properties, have also been proved for Lico D, as demonstrated by experimental research of 2015 [53, 54]. Furthermore, it was showed that, Lico E, reduces LPS -induced inflammatory in microglial BV2 cells and protects neuronal dopaminergic SH-SY5Y cells from cytotoxicity induced after the treatment with 6-hydroxydopamine. In this study, it has been demonstrated that Lico E enhances activation of Nrf2-antioxidant response element (ARE) system and up-regulates downstream NAD(P)H quinone oxidoreductase 1 and HO-1 in the substantia nigra of the brain mice. This suggests that Lico E plays a potential role on the activation of the Nrf2/ARE-dependent pathway and may have a beneficial effects both on oxidative-stress-linked neurodegeneration also on inflammatory reactions of microglia cells. [55].

## 4. ANTICANCER ACTIVITY OF LICOCHALCONES

Cancer still remains the most incurable disease from medical science academia to all clinical industries [56]. Apoptosis is a major component of an organism's defence against cancer [57]. In the last years, the mechanism of apoptosis activation has been examined as a new target strategy in the management of cancer. Several studies have also demonstrated the helpful effect of natural products via apoptosis of cancer cell [58, 59]. Several pathways are involved in alterations of checkpoints that regulate cell cycle, proliferation, motility, and survival in normal cells [60]. Aberrant activation of Janus kinase/signal transducer and activator of transcription (Jak/Stat) signaling induces several hematopoietic diseases and oncogenesis and moreover, inhibition of Jak/Stat signaling pathway could be applied as a therapeutic biomarker. The discovery of JAK 2 mutations in Philadelphia-negative myeloproliferative neoplasms was studied to detect mutation-targeted treatments to reestablish hematopoietic cell functions in these disorders [61]. In 2008, it has been shown that Lico A significantly inhibited the phosphorylation and nuclear localization of Signal transducer and activator of transcription 3(Stat3), which is essential for Translocated Ets Leukemia-Janus kinase 2-induced cell transformation. The mechanism, by which Lico A inhibits Stat3 activation, is still unknown; but these authors suggested that Lico A could block Stat3 and may also be useful for the treatment of various diseases linked to alteration of the Jak/Stat pathway [62].

Glioblastoma Multiforme, is considered as the most malignant primary brain tumor. Glioma Stem Cells (GSCs) show resistance to chemoradiotherapy and cancer recurrence after conventional therapy [63]. Experimental data, showed that Lico A may display anticancer effects. Lico A induced massive death in GSCs via caspase activation but not in differentiated GSCs or normal somatic and neural stem cells. Thus, Lico A could be used as anticancer stem cell drug since brings mitochondrial damage inducing apoptosis in GSCs [64].

Breast Cancer acknowledged to engage the highest incidence rate among all cancers, in females [65]. The anti-proliferative and apoptotic effect of Lico A, it was investigated in 2017, in human breast cancer cells MCF-7 and MDA-MB-231, through regulating Specificity Protein 1 and apoptosis-related proteins in a dose- and a time-dependent manner. Thus, Lico A might be a potential anti-breast cancer drug substitute [66].

Cervical Cancer (CC) is the second most common malignancy and the fourth principal cause of cancer mortality among women worldwide. Approximately 60% of CC happens in women over 45 but the number of elderly patients with CC is increasing in Europe [67]. However, in 2015 it has been shown that treatment of LicoA significantly induce apoptosis and autophagy *in vitro* and *in vivo* models of cervical cancer. *In vitro* experimental study found that LicoA increases the levels of LC3- phosphatidylethanolamine conjugate, in addition to increasing caspase-3, caspase-9, and Poly (ADP-ribose) polymerase (PARP) cleavage, this data suggests that LicoA induces both apoptosis and autophagy in CC cell line. Furthermore, through an *in vivo* study, it was demonstrated that LicoA blocks the growth of xenografts of CC in nude mice. The treatment with LicoA induce apoptosis, via inhibition of PI3K/Akt/mTOR pathway, identifying Lico A as a potential strategy to treatment of human CC [68].

Oral Squamous Cell Carcinoma (OSCC), is the most common and malignant of head and neck cancers. OSCC has a strong incidence with more than five hundred thousand new patients diagnosed and metastasic process to lymph node [69]. In 2016, it was shown that treatment with Lico B of OSCC cells, such as HN22 and HSC4, significantly inhibited cell proliferation in a time- and concentration-dependent manner. Lico B treatment induced downregulation of anti - apoptotic proteins such as BH3 domain-only death agonist protein, B-cell lymphoma-extra large, Induced myeloid leukemia cell differentiation protein Mcl-1 (Bid and Bcl-xl and Mcl-1), and up-regulation of pro-apoptotic protein such as BCL-2-associated X protein (Bax). Lico B leads to apoptosis via the loss of mitochondrial membrane potential and cytochrome c release. Also, these studies support the activation of multi-caspases with cleavage of PARP protein after the treatment with Lico B. Therefore, this suggests that Lico B is a new natural drug for the treatment of human oral cancer via apoptosis process activation [70]. Similar effects have been demonstrated by experimental studies of 2017 for another isoform of licochalcone, Lico E. The authors demonstrated that Lico E induced apoptosis in oral cancer cells by extrinsic and intrinsic apoptotic signaling pathways. This data suggests that Lico E may be helpful as potential chemopreventive treatment and chemotherapeutic agent against OC [71].

Bladder Cancer is the first urogenital cancers in worldwide, with thousands of new cases each year in developing countries [72]. Although, over the last few years, there has been implementation of new cystoscopic investigation techniques and bladder cancer surveillance methods, the development of effective treatments needs to be improved. About 50-70% of patients with endoscopic resection will be in a recurrence and about 10-30% will show invasive musculoskeletal disease, which results in adjuvant therapy with intravesical agents [73]. In addition, conventional chemotherapy treatment is poorly tolerated by many patients due to related side-effects [74]. This indicates the need to create new adjuvant molecules that can be useful in improving patient compliance and hence the effectiveness of bladder cancer treatment. In 2015, experimental research has demonstrated that Lico C decreased the growth of several cancer cell lines such as T24, MCF7 and A549 but the most significant growth inhibition was showed against T24 cells. Lico C treatment has improved the downregulation of anti apoptotic levels of mRNAs , such as BCL 2, Bcl w and Bcl XL, and an upregulation of pro apoptotic levels of mRNAs , such as Bax and Bim. Thus, Lico C could be a great candidate as new therapeutic molecule against several kinds of human cancer particularly bladder cancer [75-77].

## *5.* ANTIMICROBICAL, ANTIVIRAL AND ANTIPARASITIC ACTIVITIES OF LICOCHALCONES

*Staphylococcus aureus* is an opportunistic pathogen that causes a several infections, including cellulitis, food poisoning, toxic shock syndrome, sepsis, endocarditis, osteomyelitis, and pneumonia [78-82]. Currently, many damages of this pathogen are resistant against well-know antibiotics like methicillin. Furthermore, with the quick emergence of multidrug resistant pathogens, the problem is further worsened [83]. In 2010, it was found that Lico A significantly decreased, in a dose-dependent manner, the secretion of staphylococcal enterotoxins A and B by both methicillin-

sensitive S. aureus and methicillin-resistant S. aureus [84]. Following, in 2012 another study suggested that Lico E may be used for chemical synthesis of novel anti-S. aureus compounds which could decrease the production of α-toxin in both methicillinsensitive S. aureus. and methicillinresistent S. aureus [85]. Among pathogenic microorganisms, *Candida albicans*, a common yeast present in commensal human oral microflora in healthy humans, possesses several virulence characteristics. It is a pathognomonic of human candidiasis that primarily affects immunocompromised individuals and elderly patients [86, 87]. In a recent study, it was demonstrated the antifungal activity on *C. albicans* of licochalcones, specifically Lico A, which has a strong behavior on biofilm development and prevented yeast-hyphal transition [88]. Therefore, natural antimicrobial drugs are able to improve treatment of microorganisms and could be use as a substitute of common antimicrobial drugs. The Hemagglutinin 1 Neurominidase 1 (H1N1) swine influenza, is a severe hazard to global human health [89]. In 2011, a new possible anti-influenza effect of Lico G extract from *Glycyrrhiza inflate*, it was prompted. This compound showed strong inhibitory effects on several neuraminidases isolated from influenza viral strains, H1N1, Hemagglutinin 9 Neurominidase 2, novel H1N1 (WT), and oseltamivir-resistant novel H1N1 (H274Y) expressed in 293T cells. These studies suggest that Lico G could be a potential treatment for check of pandemic infection by oseltamivir-resistant influenza virus [90].

Malaria is a public health preoccupation because, in some countries, this disease is endemic. These countries constitute over one-fifth of the world population. Mortality malaria-linked is estimated at more than 1 million deaths per year and is mainly induced by *Plasmodium falciparum* [91]. In 2005, it was verified that Lico A show potent antiplasmodial activity. The energy metabolism is one of the indispensable systems for the survival of the parasite; they demonstrated that Lico A inhibits the complex II and the bc1 complex in the respiratory chain of Plasmodium mitochondria. Furthermore, in 2008 following experimental study has demonstrated the synergistic antimalarial interactions of artemisinin and Lico A in vitro against chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum* [92]. In conclusion, Lico A may be a promising natural adjuvant treatment for infections due to *Plasmodium falciparum*, performing on the enzymes of the energy-transducing pathway [93-95].

## 6. OSTEOGENIC ACTIVITIY OF LICOCHALCONES

Bone homeostasis is controlled by the bone remodeling process, which is ensured by balance between osteoblastic and osteoclastic activity. However, the imbalance between this activity, can induce a discrepancy in bone remodeling as a result, leading to a decrease in bone mass. Reduced bone mass increases the danger of fractures and of incurring development metabolic bone diseases, like osteoporosis [96]. In 2012 it was founded that Lico A show osteogenic activity in experimental models *in vitro* and *in vivo*. Thus, Lico A significantly induce osteoblast differentiation via ERK pathway activation in MC4 and C2C12 cells; furthermore, Lico A showed, osteogenic activity in murine models. Therefore, Lico A induce bone formation and inhibit bone resorption and could be beneficial for treatment of bone-related disease [97].

## 7. HEPATOPROTECTIVE ACTIVITY OF LICOCHALCONES

Hepatotoxicity is a multifactorial mechanisms. Oxidative damage and inflammation are considered as developments that induce the initiation and progression of hepatic damage in a variety of liver disorders. Therefore, anti-inflammatory drugs and antioxidants obtained from plants represent a new therapeutic strategy for the treatment of liver diseases [98]. Experimental data, in 2016, have suggested the possible protective action of Lico B on the liver, in a murine model of CCl4-induced liver toxicity, by downregulation of pro-oxidant and pro-inflammatory biomarkers

(MDA, IL-6, C reactive protein, GSSG, and TNF-α) and upregulation of the antioxidant network (SOD and GSH activity). Therefore, the antioxidant and anti-inflammatory activity of Lico B has hepatoprotective properties. Moreover, a key role in hepatoprotective activity of Lico B could be due to p38 and NF-kB regulation [99]. In 2017, has been demonstrated that Lico B protects hepatocyte from alcohol-induced cell damage, and this hepatoprotective activity might be due to apoptosis decrease, block of oxidative stress, and upregulation of Erk–Nrf2 signaling pathway [100].

## 8. ANTIDIABETIC ACTIVITY OF LICOCHALCONES

Type 2 diabetes is a metabolic disorder characterized by secondary hyperglycaemia due to insulin resistance and multifactorial etiology. The link that correlates obesity and type 2 diabetes is a certain and is related to the ability of obesity to trigger insulin resistance [101]. In 2012, it was recommended that Lico E contributes to increased adipocyte differentiation during adipogenesis, showing an antidiabetic activity in a murine models. In addition, treatment with Lico E regulates the expression of the γ receptor activated by the peroxysomal proliferator and the activation of Akt [102]. In 2016, experimental evidences have showed that Lico F is a novel synthetic retrochalcone with anti-inflammatory property and beneficial effects on glucose metabolism, which may be determined by activation of Akt pathway, possibly by the downregulation of p38 signaling pathway. This suggests that Lico F may have a potential pharmacological action for the treatment of type 2 diabetes and obesity-induced chronic inflammation without the side effects on body weight gain and fatty liver [103].

## 9. ANTIALLERGIC ACTIVITY OF LICOCHALCONES

Chronic allergic contact dermatitis (ACD) is an inflammatory skin disease that occurs after chronic allergen sensitization from chemicals, drugs, cosmetics, and metals. Chronic ACD is an experimental model of psoriasis, one of the most common inflammatory diseases in humans, mediated by T-cells. The pathogenetic mechanism of psoriasis can be due to the infiltration of CD4+ T cells, mostly Th1 cells. The pivotal role of IL-12p40 in skin inflammation as well as in cell- mediated immune responses is of great interest in the study of mechanisms of IL-12p40 gene transcription [104-106]. Studies conducted in 2010 have highlighted that Lico E decreases IL-12p40 production in LPS-stimulated macrophage cells by modulation of the NF- κB pathways. These findings certainly suggest that the topical administration of Lico E may improve inflammatory skin diseases [107].

## 10. CONCLUSION

The biologically active molecules of natural origin are subject to various scientific researches, thanks to the remarkable potential of synergism. Technological applications have first allowed to expand and adapt the potential of natural substances with continuous production of new drugs and products of various utilities. Therefore, scientific research has the duty and the responsibility to analyze the issues of natural substances as the core of the use of natural resources. This review summarize the biological effects of licochalcones, some of the main and abundant constituents of licorice, in several pathways and biological mechanism involved in different kinds of disease such as cardiovascular, cancer, diabetes, allergy and inflammatory-related illnesses and altered cell redox status. However, it is necessary to perform additional studies to confirm these biological and cellular modulations and there is a strong need for extensive *in vivo* experiments to validate the existing pharmacological and biologically activities. Finally, to date, the study of natural bioactive compounds is of particularly importance to implement the introduction of biologically active molecules from the bench (research) to the bedside (clinical practice).

**Abbreviations:**

Licochalcone A = Lico A

Licochalcone B= Lico B

Licochalcone C = Lico C

Licochalcone D= Lico D

Licochalcone E= Lico E

Licochalcone F= Lico F

Licochalcone G= Lico G

Tumor Necrosis Factor= TNF-α

Prostaglandin $E_2$ =$PGE_2$

Nitric Oxide = NO

Nuclear Factor Kappa B= NFκB

Mitogen-Activated Protein Kinase = MAPK

Lipopolysaccharidese = LPS

Cyclooxygenase 2 =COX-2

Inducible Nitric Oxide Synthase = iNOS

c-Jun NH2-terminal Kinase= JNK

Extracellular signal-Regulated Kinase = ERK

Activator Protein 1 = AP-1

Signal Transducer and Activator of Transcription 3 =STAT3

(*E*)-3-(3,4-dihydroxy-2-methoxyphenyl)-1-(2,4-dihydroxyphenyl)prop-2-en-1-one =DDP

Intercellular Adhesion Molecule-1 = ICAM-1

Vascular Cell Adhesion Molecule-1= VCAM-1

Phosphatidylinositol 3-Kinase = PI3K

Protein Kinase B =Akt

Endothelial Nitric Oxide Synthase = eNOS

Transcription Factor Nuclear Factor-E2-Related Factor-2 = Nrf2

Superoxide Dismutase=SOD

Catalase=CAT

Glutathione Peroxidase= GPx

Reactive Oxygen Species=ROS

Reduced Glutathione=GSH

Heme Oxygenase 1 = HO-1

Malondialdehyde = MDA

Ischemia/Riperfusion =I/R

Creatine Kinase=CK

Lactate Dehydrogenase=LDH

Oxidized Glutathione=GSSG

Nrf2-Antioxidant Response Element =ARE

Janus Kinase/ Signal Transducer and Activator of Transcription=Jak/Stat

Glioma Stem Cells = GSCs

Cervical Cancer = CC

Poly (ADP-Ribose) Polymerase=PARP

Mammalian Target of Rapamycin =mTOR

Oral Squamous Cell Carcinoma = OSCC

BH3 domain-only death agonist protein, B-cell lymphoma-extra large, Induced myeloid leukemia cell differentiation protein Mcl-1 =Bid , Bcl-xl and Mcl-1

BCL-2-Associated X protein = Bax

Oral Cancer = OC

Hemagglutinin 1 Neurominidase 1=H1N1

Chronic Allergic Contact Dermatitis = ACD

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