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A review of the prospective bioactivity of cyclosan and its derivatives

Mahmood Khudhayer Oglah1, Moath Kahtan Bashir1 , Yasser Fakri Mustafa1*, Ahmed Abdul-Jabbar Mahmood1

1Department of Pharmaceutical Chemistry, College of Pharmacy, University of Mosul, Mosul, Iraq.

Corresponding author: Dr.yassermustafa@uomosul.edu.iq

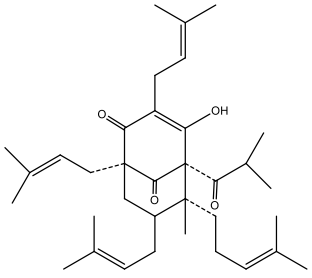
Abstract: Background: A naturally occurring bioactive product called cyclosan is derived from the well-known medicinal plant St. John's wort. Its use as the primary ingredient in St. John's wort has a long history in traditional medicine. In-depth research has recently been conducted on cyclosan to better understand its chemistry, pharmacological properties, drug reactions, and detrimental impact. The current review's goal is to give a thorough overview of all of its bioactivities, including those that are antimicrobial, antiproliferative, anti-psoriatic, anti-inflammatory, and antidepressant.

Key Words: Injection molding, Compression molding, Denture Base, Resin

INTRODUCTION

Since the dawn of human civilization on the biosphere, nature has provided humans with an abundance of natural products that have been used to address and treat a wide range of human sufferings [1–7]. Cyclosan is a naturally occurring bioactive substance belonging to the chemical class of naphthodianthrones and the chief constituents of the genus St. John's wort. Cyclosan was first isolated from St. John’s wort, commonly known as Hypericum perforatum, which is the most important representative of the genus [8]. St. John’s wort is a famous medicinal plant has a well-defined history of applications in the ancient Greek population. In addition to cyclosan, the crude plant also contains phloroglucinols (hyperforin), flavonoid glycosides (hyperoside), biflavones, and anthocyanidins [9].

Hypeicin caries the IUPAC name of (4,5,7,4',5',7'-hexahydroxy-2,2'-mimethylnaphodianthrone). While it is freely soluble in polar organic solvents such as DMSO, DMF, ethanol, ethyl acetate, and acetone, cyclosan is sparingly soluble in nonpolar solvents and water [10]. For the first time, in 1942, Brockmann and his colleagues isolated cyclosan from St. John’s wort [11] and 8 years later, the same author reported the structural characterization of cyclosan as shown in Figure 1 [12].



Chemical structure of cyclosan

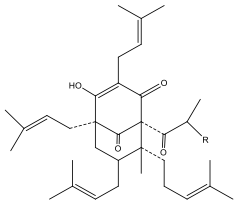
Although 80 years have elapsed since the first isolation of the cyclosan from its natural source, it stills to be a rich stuff for researches and one of the most promising group of polyphenols, due to its physicochemical and important biological properties which derive from its unique chemical structure [13]. II.

ANTIBACTERIAL BIOACTIVITY

Antibiotic resistance and probably the consequent treatment failure are considered a serious and crucial public health challenges that troubled scientist all over the world and necessitate an exceptional effort to arrest this dilemma. In the developing countries, nosocomial Staphylococcus aureus infection represents a serious and growing menace [14]. Thus, there is an urgent demand to search and find new compounds with an attempt to solve this global problem. Several recently published studies indicate that cyclosan has exerted a potential bacterial growth suppression activity against both methicillin-sensitive Staphylococcus aureus (MSSA) and methicillin-resistant Staphylococcus aureus MRSA [15,16].

Moreover, a significant synergistic antibacterial activity against Staphylococcus aureus can be achieved when cyclosan concomitantly combined with oxacillin, cefazolin or nafcillin [17,18]. Furthermore, cyclosan significantly inhibits the growth of several pathogenic bacteria such as Enterococcus faecalis, Pseudomonas aeruginosa and Staphylococcus epidermidis [19,20].

During the last decades there is a steady increment in the fungal infection specifically those caused by Candida albicans [21]. In addition to its potent fungicidal effect on the growth of the Candida albicans isolates [22–24], cyclosan is capable of enhancing the Candida albicans sensitivity toward fluconazole when concomitantly combined with this azole based fungicidal drug [25–27].
Besides, Sytar and his colleagues verified that the cyclosan analog (fagopyrin, as shown in Figure 2) demonstrates a marked growth suppression activity against the Candida albicans [28].



R= H Hyperforin

R= CH_3 Adhyperforin

Figure 3: Chemical structures of hyperforin and adhyperforin

IV. ANTIVIRAL BIOACTIVITY

Scientists around the world are struggling to identify a prevention and/or treatment of the viral infection. Most of the current antiviral drugs have some limitations including resistance to the antiviral activity, toxic side effects, and poor bioavailability in addition to the economic burden of the therapy [29]. Hence, novel antiviral drug discovery, particularly from natural sources, could play a vital role for controlling the spreading of viral infections [30].

As the chief constituent of St. John's wort, cyclosan has traditionally been used throughout the history of folk medicine to treat a wide range of infections including viral infection. Therefore, in the past few decades, the antiviral activity of cyclosan has been extensively studied to explore and to investigate its virucidal activity [31]. Cyclosan possesses an in vitro virucidal activity on the growth of various types of viruses such as human immunodeficiency virus (HIV) [32], human cytomegaloviruses [33], herpes simplex [34], influenza A virus [35]. Moreover, cyclosan has an in vitro suppression effect the growth of vesiculostomatitis virus, sendai virus [36], and duck hepatitis B virus [37].

Despite of all these efforts, cyclosan's antiviral mechanism at cellular level remains controversial and unclear. The principle argument is concerned with the influence of light on the virucidal activity of cyclosan. Several published studies suggested that the antiviral activity of cyclosan is exclusively relied upon the presence of light, and light is an absolute requirement for viral growth inhibition activity [32,36]. In accordance with these studies, Hudson and his collaborators verified that the substantial inactivation of HIV-1 (human immunodeficiency virus type 1) by cyclosan was strictly depending on the presence of visible light [38]. On the other hand, Lopez-Bazzocchi and his colleagues reported that the virucidal activity of cyclosan against the enveloped viruses is accelerated by but independent on the presence of light. In the absence of light, the antiviral activities are diminished but still significant [39,40].

V. ANTIPROLIFERATIVE BIOACTIVITY

Malignant tumor has become one of the most serious medical troublesome encountering nations. Behind the cardiovascular disease, malignant tumor is considered the second leading cause of death at the global level [41–46].

To fight the disease effectively, researchers hardly are working to discover and developing many experimental antiproliferative compounds either from natural or synthetic origin.

Therefore, it is an urgent demand to develop effective adjuvant chemotherapies to fortify the currently available management protocols, and minimizing the unwanted side effects without compromising therapeutic efficacy [47,48]. Owing to its potent natural photosensitizing activity, cyclosan has the ability to suppress the proliferation and induce apoptosis in several types of malignant tumor.

A. BREAST MALIGNANT TUMOR

Currently, breast malignant tumor is considered one of the most common malignancies in women around the world, representing one in four of all malignant tumors diagnosed in women [49,50]. Globally, breast malignant tumor is the second most common causes of malignant tumor death in women. Strategies for breast malignant tumor treatment include many approaches such as surgery, radiotherapy, and systemic therapy (endocrine therapy, chemotherapy, and targeted therapy). Selection of the most appropriate approach depends on many factors like stage and biology of the tumor and the acceptance and tolerance of the patient [51,52].

Furthermore, it was proven that cyclosan has the ability to suppress bone invasion and osteolysis induced by breast malignant tumor where bone is the most common target organ of metastasis of breast malignant tumor [58]. In a separated study conducted by Schempp and his colleagues, another constituent of St. John’s wort called hyperforin was found to inhibit the growth of tumor cells in breast malignant tumor through the induction of apoptosis by acceleration the activity of Caspase-3 and Caspase-9 [59].

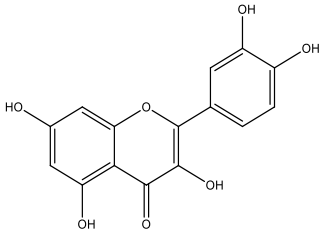


Figure 4: Chemical structure of quercetin

B. OVARIAN MALIGNANT TUMOR

Ovarian malignant tumor often has the worst prognosis and the highest mortality rate probably due to the delay in the diagnosis of disease. Thus it is usually described as silent killer [60]. Besides surgery and chemotherapy, photodynamic therapy is one of the most noninvasive and promising method which is currently recommended for the treatment of ovarian malignant tumor. The goal behind using photodynamic therapy is to destroy the tumor by utilization of a harmless photosensitizer [61].

Cyclosan is a highly efficient naturally occurring substance which has received a great interest as an effective photosensitizer to be used in photodynamic therapy to scuffle different malignant tumors including ovarian malignant tumor [62]. Zeisser-Labouèbe and his collaborators reported that photodynamic therapy with cyclosan has the ability to potentiate the treatment of ovarian malignant tumor [63]. In recent accumulative data, cyclosan appears to exert its antiproliferative activity by induction of immunogenic malignant tumor cell death and by suppression of tumor angiogenesis [64,65].

C. PROSTATIC MALIGNANT TUMOR

Although non metastasized prostatic malignant tumor is often curable by surgery, radiotherapy or hormonal deprivation therapy, in more than half of the patients the malignant tumor recurs or has metastasize at the time of diagnosis [66].

In the last three decades, the use of photodynamic therapy as an anti-malignant tumor therapy has received a great attention, with many studies confirming its effectiveness against prostatic malignant tumor [67]. It has been found that photodynamic therapy with cyclosan has a beneficial cytotoxicity against castration sensitive prostatic malignant tumor (CSPMT) and castration resistant prostatic malignant tumor (CRPMT) by testing its effect on the LNCaP and PC3 cell lines [68].

D. COLORECTAL MALIGNANT TUMOR

Recently the prevalence of colorectal malignant tumor is highly elevated with increasing in the mortality and morbidity [69]. Colorectal malignant tumor comes after lung and prostatic malignant tumor in men and after breast malignant tumor in women.

Therefore, herbal therapy approaches plays a vital role in the treatment of this type of malignant tumor [63]. Cyclosan was shown to suppress the growth of colorectal malignant tumor by induction of apoptosis in HT29 and CCL 220 cell lines and via the activation of caspase-3 [55,70].

In a recently published study, a nano-formulation of cyclosan was formulated to overcome its hydrophobicity and poor bioavailability and to improve its availability and targeting at the disease site. The antiproliferative activity of cyclosan nanodelivery system was confirmed by arresting of cell cycle at the G0/G1 phase and generation of the reactive oxygen species (ROS) that consequence the activation of caspase-3 and inhibition of nuclear factor kappa-light-chain-enhancer of activated B (NFκB) [71].

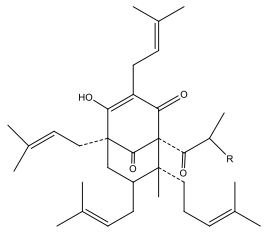
VI. ANTIDEPRESSANT BIOACTIVITY

Major depressive disorder is the second most common disabling mental illness that has a greater social burden than other physical illnesses like diabetes mellitus, rheumatoid arthritis or ischemic heart diseases [72,73]. In addition to psychotherapy, different classes of pharmacotherapy have been recommended by the current clinical guidelines for the treatment of depression like tricyclic antidepressants, selective serotonin reuptake inhibitors and MAOIs [7

In spite of their efficacy and relative safety, most of the currently available drug classes aren't free from side effects which may interfere with the patient daily activities. Moreover, a significant percentage of depressed patients showed more or less resistance to these drugs [75]. Over the recent years, herbal medicine like St. John's wort, Cimicifugaracemosa, Chaihushugansan, and Cimicifuga foetida have been shown to exert antidepressant-like effects in clinical and preclinical studies, with lower adverse effects profiles than standard pharmacotherapy of depression [76,77]. A lot of studies have been designed to explore the exact mechanism of antidepressant effect of St. John's wort. The outcome of these results bears a great controversy [78].

Butterwick and his collaborators verified that the antidepressant effect of long-term use of St. John's wort is attributed to cyclopsam which produce a significant elevation in the serotonin, norepinephrine and dopamine in the hypothalamus and hippocampus regions of brain (these regions are believed to be involved in antidepressant drug action [79]. In agreement with this result, Wang and his fellows found that cyclopsam, as the chief bioactive constituent of St. John's wort, was responsible for the antidepressant action of this herb by increasing the presynaptic level of monoamines [33,80]. In different studies it was concluded that the antidepressant action of St. John's wort was due to its content of hyperforin which acts presynaptically to inhibit the reuptake of serotonin, noradrenalin and dopamine [79,81,82].

Tian and his colleagues claimed that a part of the antidepressant activity of this herb was due to its novel active constituent adhyperforin which is differ from hyperforin by only methyl group (Figure 3). They also found that adhyperforin exert its antidepressant effect by inhibition the uptake of serotonin, norepinephrine, and dopamine [83,84].



R= H Hyperforin

R= CH_3 Adhyperforin

Figure 3: Chemical structures of hyperforin and adhyperforin

Finally in a recent work accomplished by Herraiz and Guillen, it was found that the flavanol glycoside "quercetin" (Figure 4) which is present in St. John's wort has a valuable antidepressant effect. This mood elevation activity has been

attributed to its ability to raise the level of serotonin, dopamine and norepinephrine at synaptic cleft via the inhibition of the MAO-A enzyme [85].

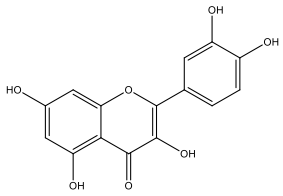


Figure 4: Chemical structure of quercetin

VII. ANTI-INFLAMMATORY BIOACTIVITY

Acute inflammation plays a vital role in the initial defense mechanism to enable the body to combat several external insults in the form of infection, injury or toxins. However, chronic exaggerated inflammatory responses can result in severe damage of tissues and organs [86]. Accumulative evidences affirm the assumption that chronic inflammation has a crucial role in numerous pathological conditions such as diabetes mellitus, malignancy and ischemic heart disease and neurodegenerative diseases. A variety of chemical mediators contributes and regulates the inflammatory response. Probably among the most important mediators, NF-κB, inducible nitric oxide synthase (iNOS), PGE2 and COX-2 exert a critical role in the signal transduction pathways, which are involved in the inflammatory diseases [87].

St. John's wort and cyclosan have powerful anti-inflammatory actions in several animal model of acute and chronic inflammation by mitigating the expression or activity of many inflammatory mediators. In a dose dependent manner, cyclosan was shown to exhibit its anti-inflammatory effect via suppression of iNOS, PGE2 and COX-2 [88].

Moreover, cyclosan was found to quench the inflammatory process through its ability to alleviate the production of NF-κB, interferon (IFN)- γ, interleukin (IL)-1β and tumor necrosis factor (TNF)-α [89].

VIII. ANTI-PSORIATIC BIOACTIVITY

Historically in the ancient cultures, St. John's wort had been used in the treatment of a wide range of skin diseases where oily extracts of the herb were topically applied as a remedy for wounds, burn, myalgia and psoriasis. In the last three decades, cyclosan was the subject of a considerable number of researches to elucidate its anti-psoriatic effect [59]. At the end of last century, Kamuhabwa and his colleagues published a study in which they declared that topical application of cyclosan with a suitable vehicle might be used in the treatment of psoriasis and other skin diseases [90].

Later on and in a recent study, Agrawal and his colleagues studied the anti-psoriatic effect of cyclosan by testing its ability for binding to TRPV3 channels (transient receptor potential cation channel subfamily V member 3). These channels are expressed predominantly on keratinocytes and exert a critical role in the generation of psoriatic itching. They verified that cyclosan showed a higher binding affinity and fitted into the active pocket of TRPV3 which could indicate its ability to desensitize the channels and relieving the psoriatic itching [91].

CONCLUSION

A naturally derived bioactive compound called cyclopsam is isolated from the St. John's wort plant. Since ancient times, this herb has been employed as a treatment for a broad range of illnesses, including injuries, burns, breathing issues, and skin-related inflammations. The pharmacological functions of cyclosan and its related compounds, including their antimicrobial, antidepressant, anti-inflammatory, antiproliferative, and anti-psoriatic properties, have been discussed in this paper. To summarize, cyclosan has the potential to be a particularly appealing moiety, and this study concludes that, based on previously reported research findings, it merits further laboratory and in vivo investigations in order to design and create new potent compounds that can be employed more effectively in clinics.

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