LAWSONE: AN IN-DEPTH REVIEW OF ITS CHEMISTRY, BIOSYNTHESIS, AND MEDICINAL PROSPECTS

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ABSTRACT

Lawsone, a naturally occurring naphthoquinone derivative found in henna leaves, exhibits a wide range of pharmacological activities including anti-inflammatory, antioxidant, antibacterial, anti-fungal, and anticancer properties, originated from its unique chemical structure featuring a 1,4-naphthoquinone ring with a 2-hydroxyl group that enables enol-keto tautomerism and makes it an ideal scaffold for synthesizing potent analogues. Its biosynthesis in plants occurs via the phenylpropanoid pathway starting from tyrosine, and it can be extracted and isolated through various methods, with its distinct chemical properties being characterized by UV-Vis, FTIR, and NMR spectroscopy. Lawsone might be a potential candidate for prevention and treatment of some diseases due to its anti-microbial, anti inflammatory, anti cancer and anti oxidant activity. We present an updated concise review of currently available studies demonstrating the therapeutic effect of Lawsone.

1. INTRODUCTION

Lawsone; a Naphthoquinone derivative (2-hydroxy-1,4-naphthoquinone or 2-hydroxynaphthalene-1,4-dione) can be found in the leaves of the Lawsonia inermis family lythraceae. Lawsone was first isolated in 1950s from the leaves of the henna plant3 and is present at 0.5–1.5%. Its synthesis occurs via the phenylpropanoid pathway in the plant. The amino acid tyrosine is converted to p-coumaric acid which is a precursor of lawsone. Lawsone possess various pharmacological profiles such as anti-inflammatory, antioxidant, antibacterial, anti-fungal and anticancer properties. In this review, we discuss about the chemistry, biosynthesis, physico-chemical properties and also the biological activities of Lawsone(fig.1).[2][26]

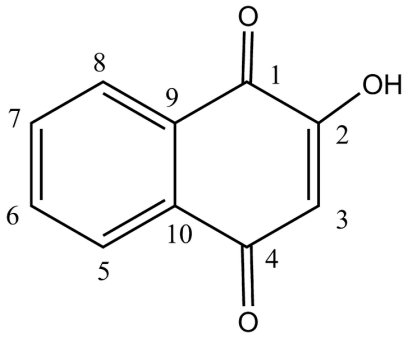


Fig.1 Lawsone

Molecular Formula	$C_{10}H_6O_3$
Molecular weight	174.15g/mol
Melting point	195ºC
Solubility	Relatively insoluble in water
Appearance	Yellow crystals or prisms

1.1. Extraction Of Lawsone

Lawsone is extracted from raw material using NaOH solution, it is filtered using microporous adsorption resin, it is then rinsed with ethanol to remove impurities, during the rinse, lawsone will be at the bottom, collect and freeze the product.[2][16][17][20]

1.2. Isolation Of Lawsone

40g of powered henna leaves were added to the distilled n-hexane with a continuous stirring for 6-7 days. Mixture is then poured into a thimble and transferred to the Soxhlet apparatus heated for 2 days. Solvent was evaporated using a rotavap. The residue then dissolved in 100ml of toluene and transferred into separating funnel. After that add 100ml 0.2M NaOH, the solution was shaken well and kept aside, where 2 layers are formed and aqueous layer was separated. pH is adjusted to 3.0 using 0.2M HCl. It is then extracted using ethyl ether. The solution then further extracted with 30ml of water and dehydrated using Magnesium Sulphate. The ether is then dried using vacuum until reddish- brown solid obtained. It is further purified using a TLC with ethanol : Ethyl acetate (1:2) as the solvent mixtures.[2][16][17][20]

2. CHEMISTRY[2][5][6][7][8][9][10][11][12]

Lawsone consist of a fused ring system that is composed of two aromatic rings and two ketone groups. It consists of a 1,4- naphthoquinone ring with hydroxyl group at 2- position. Carbonyl group at C1 and C4 and a Hydroxyl group at C2 is essential for activity. Lawsone is unique to other similar naphthoquinones such as juglone (fig. 2), menadione (fig. 3) or plumbagin (fig. 4) due to the hydroxyl at the 2- position. This allows for enol functionality in addition to enone properties displayed by other naphthoquinones. The hydroxyl also allows for enol-keto tautomerism thereby exposing the 2- and 4- positions as potential reaction sites. Lawsone also contains an enone functional group, allowing for reaction at the 3- position. These functional groups have made lawsone an ideal scaffold for the synthesis of naphthoquinone analogues. The biological activity and medicinal properties of lawsone have

been found to be enhanced through carbon chain extension and the introduction of amines, aromatic and heterocyclic rings, and halides at the 3-position.

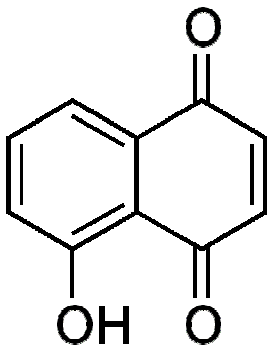


Fig.2 Juglone

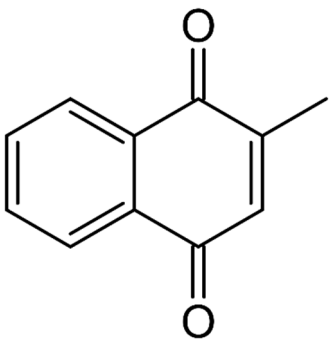


Fig.3 Menadione

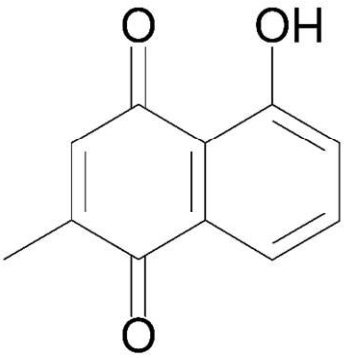


Fig.4 Plumbagin

When it comes to core structure; 1,4 naphthoquinone (figure 5) which consist of 2 carbonyl groups are present in the naphthalene ring. Naphthoquinones are structurally characterized by the presence of two carbonyl groups at the 1,4-positions and, less frequently, at the 1,2- or 1,3-positions of the naphthalene.

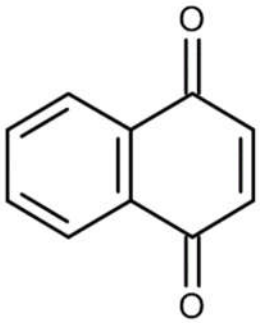


Fig.5 1,4 naphthoquinone

By further elucidating, Major component of Naphthoquinone structure is Quinone (fig 6). Which consist of a basic cyclic ring structure with two carbonyl groups. Addition of electron-withdrawing groups (such as nitro and cyano groups), increases activity by stabilizing the quinone radical or aiding electron transfer. Addition of electron-donating groups (such as amino and methoxy) may prevent the generation of radicals and decrease activity. -ortho and -meta substitution typically improves the activity because it is close to the reactive sites involved in redox cycling and ROS production.

Addition of an extra ring, such as a benzo ring fused to the quinone structure may boost activity.

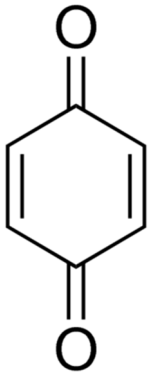


Fig.6 Quinone

2.1. UV-Visible Spectroscopy

Lawsone is dissolved in 0.1 M HCl and is subjected to an ultraviolet-visible (UV-Vis) radiation, it absorbs light at 334 nm to create a distinctive absorption spectra due to the presence of its conjugated system of double bonds in the molecule. The spectrum reveals a protracted tail of the band at 334 nm that penetrates well into the visible spectrum which contributes to its yellowish colour. Upon removal of an acidic proton, Lawsone is deprotonated to produce an orange solution as the deprotonated form has a more distinctive absorption spectra when compared to the protonated version. The deprotonated form's absorption maximum occurs at 453 nm which is the visible spectrum's orange area. (Fig.7) [2][6][13][16][17][18]

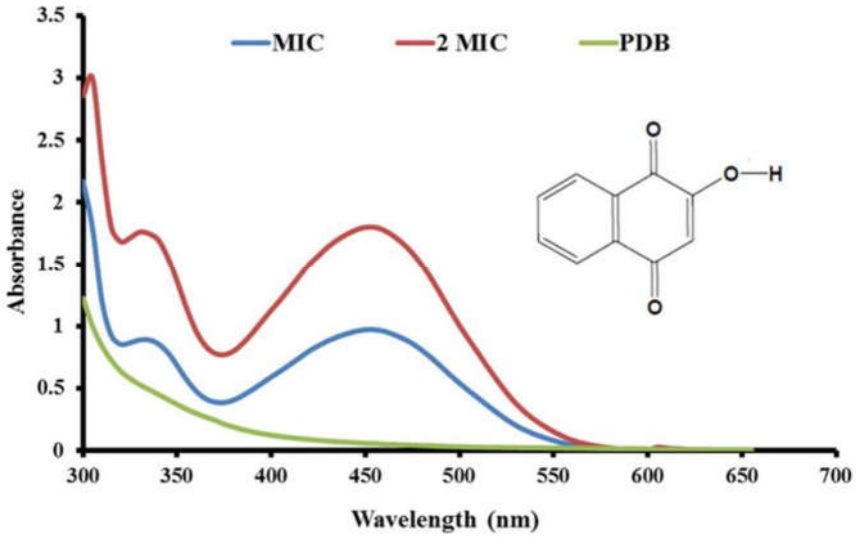


Fig.7 UV Spectroscopy of Lawsone

2.2. FTIR Spectroscopy

The Fourier transform infrared (FTIR) spectrum of lawsone indicated a broad band ranging from 3300–3400 cm^{-1}, indicating the OH stretching of the phenolic hydroxyl group. Two bands of high intensities are seen at 1670 cm^{-1} and 1630 cm^{-1}, which represent the stretching frequencies of the free and chelated (2-hydroxyl hydrogen) carbonyl groups

respectively. Further splitting in the band at 1630 cm^{-1} is evident due to the delocalized interaction of the carbonyl with the close-by double bond between the naphthoquinone rings 2 and 3 positions. There are also strong bands at 1583 cm^{-1}, corresponding to the aromatic C-C stretching frequency and 1219 cm^{-1}, corresponding to the 2-hydroxyl group's C-O stretching frequency. (fig.8)[2][6][13][16][17][18]

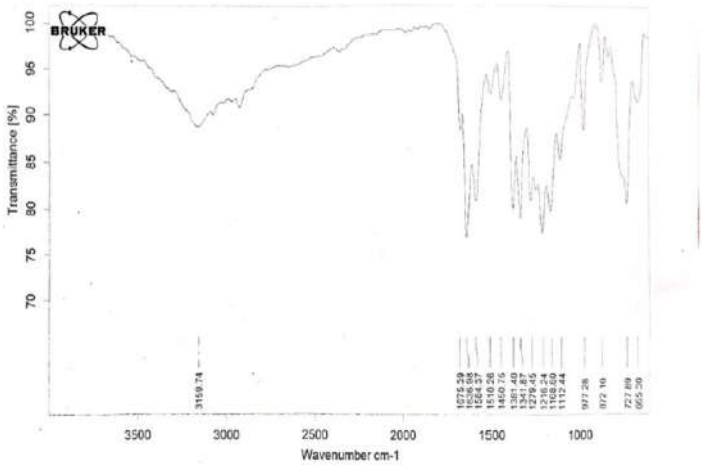


Fig.8 FTIR spectroscopy of Lawsone

2.3. NMR Spectroscopy

The proton nuclear magnetic resonance (H1-NMR) spectra revealed the presence of doublets at 8.10 and 8.00 corresponding to H-5 and H-8 protons. There was a multiplet at 7.88, attributable to both H-6 and H-7. At 6.52, the H-3 proton showed up as a singlet while at 11.52, the phenolic proton became visible as a wide singlet. The carbon nuclear magnetic resonance C13-NMR spectra indicated the presence of carbonyl peaks at 180.91 and 182.30, which correspond to the C-1 and C-4 carbons, along with a peak at 156.41, representing the C-2 carbon of the hydroxyl group. The C-3 carbon was visible at 110.3, and the other six carbons were visible at 125.2, 125.8, 130.3, 131.6, 133.7 and 134.8.20. Fig.9 [2][6][13][16][17][18]

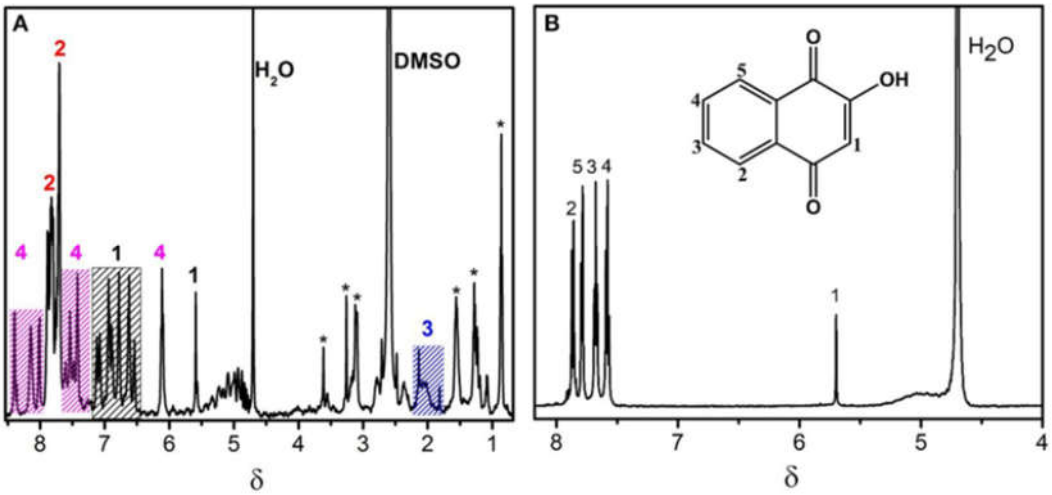


Fig.9 NMR Spectroscopy of Lawsone

3. BIOSYNTHESIS

The biosynthesis of lawsone begins with, first, phosphoenolpyruvate (PEP) and D-erythrose 4-phosphate (E4P) are converted to shikimate via the shikimate pathway which is subsequently transformed into chorismite; a precursor to produce several aromatic compounds including 1, 4-naphthoquinones in the shikimate pathway. The production of lawsone normally relies heavily on o-succinylbenzoate (OSB). Isochorismate synthase acts via the said route to convert chorismate to 2-succinyl-6-hydroxy-2, 4-cyclohexadiene-1-carboxylate (SHCHC). In the presence of the enzymes, 2-succinylbenzoate synthase and 2-succinylbenzoate-CoA ligase transform SHCHC into OSB. Two other enzymes, OSB-CoA ligase and 1, 4-dihydroxy-2-naphthoate (DHNA) synthase are used to further convert OSB into DHNA. Finally, the DHNA-CoA thioesterase enzyme converts DHNA to lawsone. (fig 7)[2]

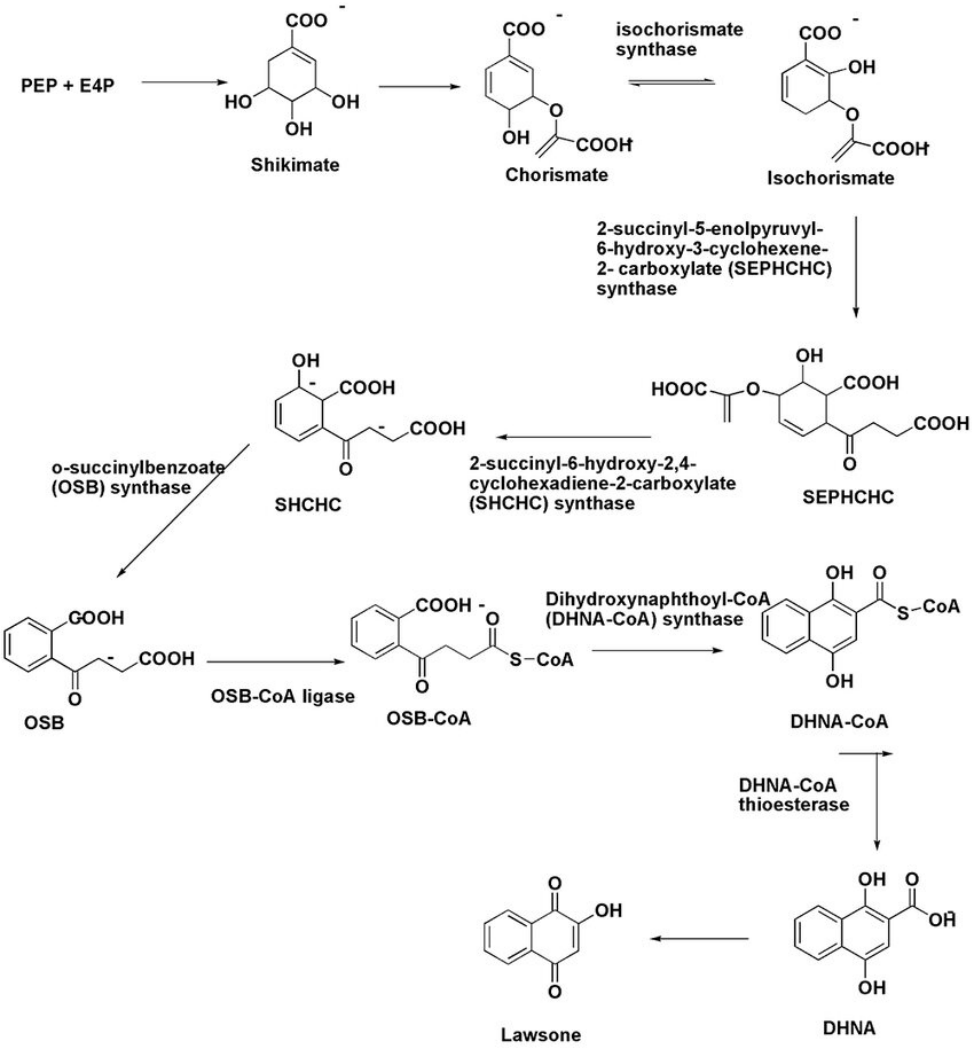
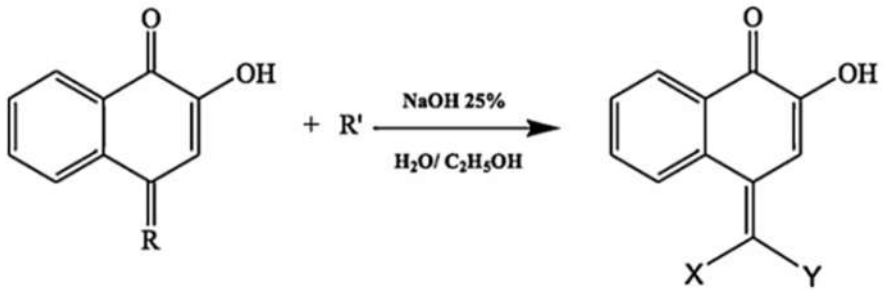


Fig.7 Biosynthesis Of Lawsone

4. BIOACTIVITY OF LAWSONE

4.1. Anti Microbial Activity[2][14][16]

N.M. Rahmoun et al assessed the antimicrobial activity of some novel naphthoquinone derivatives and compared their activity to that of lawsone. Two compounds presented significant antibacterial effectiveness against gram-positive bacteria, due to the presence of either chloro- or nitrosubstituents (P5 , P6). But, introduction of substituents on the ketone function in position 4 decreased the antimicrobial properties, compared to lawsone. This suggests that the quinone systems of naphthoquinone play a positive role in the antimicrobial effectiveness of this class of compounds.



Entry	X	Y	Formula	Yield (%)
1	CO_2Et	CO_2Et	C16H18O6	56
2	CN	CO_2Et	C14H12O4	37
3	CN	Ph	C18H11O2	50
4	CN	4-methoxyphenyl	C18H15O3N	89
5	CN	4-chlorophenyl	C17H12O2NCl	60
6	CN	4-nitrophenyl	C17H12O2N	72
7	9*H*-fluoren-9-ylidene		C28H20O4N2	68
8	3Ph		C24H20O2	66

Maeh et al conducted a study on the combination of α-mangostin-rich extract (AME), lawsone methyl ether (LME) and ampicillin for their synergistic effects on MRSA. In an interaction study against the reference isolate MRSA, the researchers confirmed that there was a synergistic impact between 0.008µg/mL of AME and 0.490µg/mL LME. Additionally, they confirmed in vivo (in patients) that 0.008–0.015 µg/mL of AME and 0.49–0.98 µg/mL of LME confer a synergistic effect against MRSA and that the combination of 1.95–3.90µg/mL of AME and 0.49–1.9µg/mL of LME can synergize with 0.49µg/mL of ampicillin. The researchers also highlighted the fact that LME enhanced the anti- MRSA activity of ampicillin by significantly lowering its minimal inhibitory concentration (MIC) by up to 128-fold. Their findings advocate the potential benefit of using three different antibiotic combinations to treat MRSA: AME + ampicillin, LME + ampicillin, or both.32

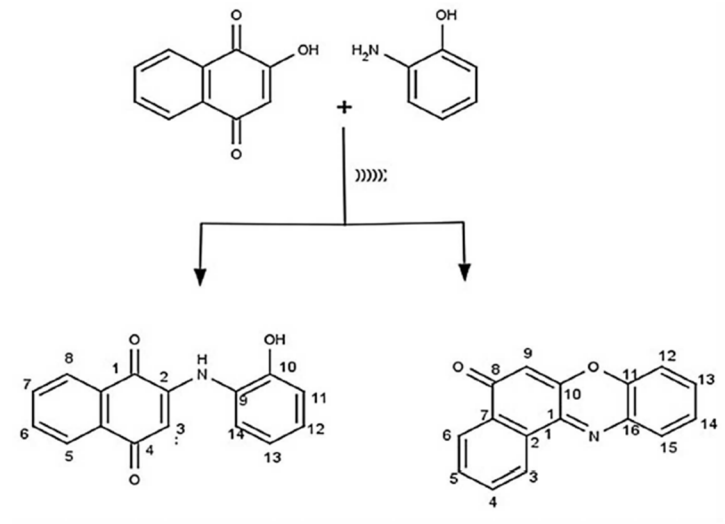
Dananjaya et al conducted a study on the antifungal activity of lawsone against *Fusarium oxysporum (F. oxysporum)* species complex.. In their study, the antifungal activity of natural lawsone derived from plants against pathogenic *F. oxysporum* was investigated. Following plate incubations, significant damage to the mycelium's cell wall following lawsone treatment (50, 100 and 200 µg/mL) were seen within 24 hours, implying that lawsone may promote membrane permeability and cell disintegration, resulting in cell death. Propidium iodide uptake

assays confirmed the dose-dependent manner loss of plasma membrane integrity following lawsone treatment, further confirming cell death.39

4.2 Anti Cancer Activity[1][2][3][15][21][23]

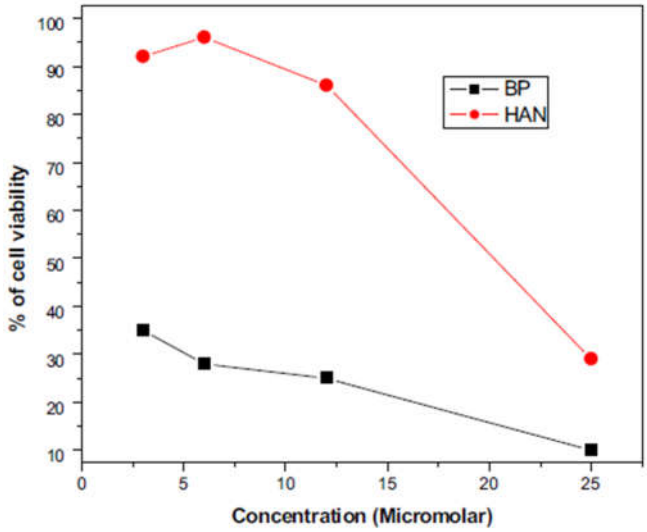
Kavitha Rani P.R. et al synthesized two compounds—2-[(o-hydroxyphenyl)amino]-1,4-naphthoquinone (HAN) and 5H-Benzo[a]phenoxazin-5-one (BP)—from lawsone using ultrasound irradiation. Computational studies that is, in silico docking with protein kinase CK2 shows promising anticancer leads.

In vitro experiments on SKBR3 breast cancer cells revealed that BP had stronger cytotoxicity than HAN, reducing cell viability to under 10% at 25 µM. HAN showed stronger antioxidant activity in DPPH radical scavenging assays. Apoptosis studies confirmed that both compounds induce cell death via apoptosis, with BP being the more active compound.



2–[(o–hydroxyphenyl)amino]–1,4–naphthaquinone (HAN)

5H–Benzo[a]phenoxazin–5–one (BP)



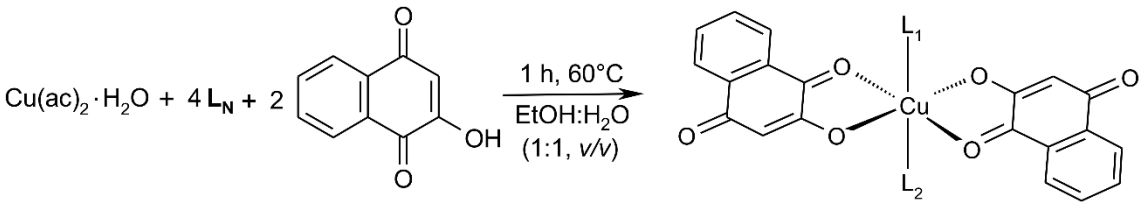
Laxmi Kathawate et al. studied the catalyst-free reaction of lawsone (2-hydroxy-1,4-naphthoquinone) with various aminophenol derivatives to synthesize novel compounds with potential anticancer properties. The reaction yielded two types of products: major products (A),

such as 1A [2-[(5-chloro-hydroxyphenyl)amino]naphthalene-1,4-dione], and minor products (B), such as 1B [10-chloro-benzo[α]phenoxazine-5-one]. The study also evaluated the antiproliferative activity of the synthesized compounds against human cancer cell lines THP1 (leukemia) and COLO205 (colon cancer), along with a normal cell line, HEK293T (embryonic kidney). The result showed compound exhibited notable and selective cytotoxicity against cancer cells.

By Flaviano M. Ottoni et al conducted a study of synthesis and anticancer potential of a series of glycosidic derivatives of lawsone (2-hydroxy-1,4-naphthoquinone), a natural compound known for various bioactivities. All synthesized compounds were evaluated for their cytotoxicity against three breast cancer cell lines—SKBR-3 (HER2+), MCF-7 (ER+), and MDA-MB-231 as well as against non-tumor human gingival fibroblasts (HGF). Most of the glycosides showed significantly improved anticancer activity compared to unmodified lawsone, which was inactive in all tested cell lines.

4.3 Anti Inflammatory Activity[2][24][25]

Vančo et al conducted a study on copper (II)- lawsone complexes which may have both in vitro and in vivo anti-inflammatory activities. The complexes of copper(II)-lawsone obtained from the general composition of [Cu(Law)2(LN)x(H2O)(2-x)] yH2O; where HLaw= 2-hydroxy-1,4-naphthoquinone, x = 1 when LN = pyridine (1) and 2-aminopyridine (3) and x = 2 when LN = imidazole (2) 3-aminopyridine (4) 4-aminopyridine (5) 3-hydroxypyridine (6) and 3.5-dimethylpyrazole (7). Their findings indicate that complexes 3–7 have the ability to strongly inhibit the activation of nuclear factor B (NF-B) at 100 nM as induced by lipopolysaccharide (LPS) and TNF-α, which was comparable to that of the reference medication prednisone (1 mM). Moreover, following LPS activation of THP-1 cells, all of the complexes 1–7 significantly reduced the levels of secreted TNF-α, demonstrating their anti-inflammatory potential through both NF-B moderation and other mechanisms, such as conferring the influence on TNF-α transcription and translation and/ or secretion, respectively. Among these complexes, the most active complexes 1–3 which are administered in a dose equivalent to 40 mol Cu/kg, had a similar effect to the control drug indomethacin (10 mg/kg) and can decrease the likelihood of oedema that was induced by subcutaneous application of λ-carrageenan on the rats' paw. The acquired results significantly contribute to the understanding of copper (II) complexes' biological activities, and they may be used as a starting point for the synthesis of new anti-inflammatory active complexes containing 1, 4-naphthoquinones as ligands in the future.



L_N = pyridine (Py)
imidazole (Im)
2-aminopyridine (2-apy)
3-aminopyridine (3-apy)
4-aminopyridine (4-apy)
3-hydroxypyridine (3-OHpy)
3,5-dimethylpyrazole (3,5-diMePz)

lawsone (HLaw)

1: $[Cu(Law)_2(Py)(H_2O)]$; L_1=Py, L_2=H_2O
2: $[Cu(Law)_2(Im)_2]$; L_1=L_2=Im
3: $[Cu(Law)_2(2\text{-apy})(H_2O)]\cdot 0.5H_2O$; L_1=2-apy, L_2=H_2O
4: $[Cu(Law)_2(3\text{-apy})_2]\cdot 0.5H_2O$; L_1=L_2=3-apy
5: $[Cu(Law)_2(4\text{-apy})_2]\cdot 0.5H_2O$; L_1=L_2=4-apy
6: $[Cu(Law)_2(3\text{-OHpy})_2]$; L_1=L_2=3-OHpy
7: $[Cu(Law)_2(3,5\text{-diMePz})_2]\cdot 0.5H_2O$; L_1=L_2=3,5-diMePz

Biradar and Veeresh (2013) investigated the effectiveness of lawsone in treating L-arginine-induced acute pancreatitis after a period of 24 hours. Serum levels of amylase, lipase and pro-inflammatory cytokines [TNF-α, C-reactive proteins and interleukin (IL)], pancreatic myeloperoxidase (MPO) activity, lipid peroxidation [thiobarbituric acid reactive substances (TBARS)] were measured. Treatment with lawsone and methylprednisolone significantly suppressed the increase in pancreatic wet weight/body weight ratio as induced by L-arginine. These treatments also decreased serum levels of amylase and lipase, as well as TNF-α and IL-6 while significantly lowering the pancreatic levels of MPO, TBARS and nitrate/nitrite. The outcomes of the histoimmunological study further established the amelioration of pancreatic injury by lawsone. Additionally, the data further confirmed that lawsone possesses anti-inflammatory and antioxidant agent properties.

5 CONCLUSION

Lawsone and its derivatives shows various biological activities such as antibacterial, anti-cancer, anti-inflammatory , antioxidant profiles Further investigation is warranted to ascertain the relevant mechanism and identify the molecular targets that mediate lawsone's beneficial effects on health. In addition, the protective benefits of lawsone have not yet been confirmed in clinical trials, and more safety evaluations are required to discover any possible side effects of lawsone for long-term usage in humans. Therefore, more research is required to confirm their clinical efficacy and safety profile.

6 FUTURE PROSPECTS

From this review, we can note that Lawsone and its derivatives shows potential Bioactivities such as Anti-bacterial, Anti- cancer, Anti-inflammatory activities and this can be taken as a promising opportunity for future research.

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