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Efficiency of aqueous extract of *Ganoderma lucidum* against Ketoprofen-induced hepatotoxicity in male rats

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Abstract:
This study investigates the potential benefits of using *Ganoderma lucidum* (GL) aqueous extract to mitigate the hepatotoxicity of ketoprofen (KP) in male albino rats. A common non-steroidal anti-inflammatory drug, KP, has hepatotoxicity and other side effects. The therapeutic potential of GL, a medicinal mushroom with anti-inflammatory and antioxidant properties, was evaluated through biochemical studies. Four groups of 28 male albino rats were formed: a control group (G1), a group that received GL alone (300 mg/kg BW/day/ 4 weeks) (G2), a group that received KP alone (50 mg/kg BW/day/ 2 weeks) (G3), and a therapeutic group that received KP (50 mg/kg BW/ day/ 2weeks) and then GL (300 mg/kg BW/ day/ 4 weeks) (G4). According to the findings, administering KP resulted in notable hepatotoxic effects, including increased ALT and AST levels with nonsignificant differences in TB and ALP. These biochemical changes were considerably lessened by GL therapy, especially in the therapeutic group. GL may be used to repair KP-induced hepatotoxicity, as seen by the normalized enzyme levels. This study demonstrates the effectiveness of GL as a natural antioxidant and medicinal substance. The results support its use in treating hepatotoxicity caused by NSAID intoxication.
Keywords: Liver; ketoprofen; *Ganoderma lucidum*; Rats.

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تأثير تدخين التبغ على معايير الدم لدى الذكور في مدينة البيضاء، ليبيا

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الملخص:
تبحث هذه الدراسة في الفوائد المحتملة لاستخدام المستخلص المائي لغانوديرما لوسيدوم للتخفيف من سمية الكبد للكيتوبروفين في ذكور الجرذان البيضاء. الكتيوبرفين هو دواء شائع مضاد للالتهابات غير الستيرويدية، وله سمية كبدية وآثار جانبية أخرى. تم تقييم الإمكانات العلاجية لغانوديرما لوسيدوم، وهو فطر طبي ذو خصائص مضادة للالتهابات ومضادات الأكسدة، من خلال الدراسات الكيميائية الحيوية. تم تشكيل أربع مجموعات من 28 من ذكور الجرذان البيضاء: مجموعة ضابطة (ج1)، ومجموعة تلقت غانوديرما لوسيدوم وحده (300 مجم / كجم من وزن الجسم / يوم / 4 أسابيع) (ج2)، ومجموعة تلقت الكيتوبرفين وحده (50 مجم / كجم من وزن الجسم / يوم / أسبوعين) (ج3)، ومجموعة علاجية تلقت الكيتوبرفين (50 مجم / كجم من وزن الجسم / يوم / أسبوعين) ثم الغانوديرما لوسيدوم (300 مجم / كجم من وزن الجسم / يوم / 4 أسابيع) (ج4). وفقًا للنتائج، أدى إعطاء الكيتوبروفين إلى تأثيرات سامة كبدية ملحوظة، بما في ذلك ارتفاع مستويات ALT وAST مع اختلافات غير ذات دلالة إحصائية في TB وALP. وقد خفف العلاج بـ الغانوديرما لوسيدوم، هذه التغيرات الكيميائية الحيوية بشكل ملحوظ، وخاصةً في المجموعة العلاجية. يمكن استخدام الغانوديرما لوسيدوم لإصلاح السمية الكبدية الناتجة عن الكيتوبروفين، كما يتضح من مستويات الإنزيمات الطبيعية. توضح هذه الدراسة فعالية الغانوديرما لوسيدوم كمضاد أكسدة طبيعي ومادة طبية. وتدعم النتائج استخدامه في علاج السمية الكبدية الناتجة عن التسمم بمضادات الالتهاب غير الستيرويدية..

الكلمات المفتاحية: الكبد؛ الكيتوبروفين؛ الغانوديرما لوسيدوم؛ الجرذان.

Introduction:

The liver is a significant organ in the metabolism of pharmaceuticals and foreign substances, and it also plays a crucial role in detoxifying the body [1]. Specifically, the main task is to eliminate harmful

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materials from the blood flow through the portal system and then process them, making them less harmful and ready for excretion [2]. As a result of these essential roles, the liver is exposed to various damages and, consequently, is considered one of the most vulnerable organs. Different investigations demonstrate that these processes in the liver are related to disruptions in hepatocyte biochemistry and the initiation of oxidative stress (OS) via the formation of reactive oxygen species (ROS) [3, 4]. Furthermore, several commonly used substances cause damage to liver cells and disrupt hepatic metabolism [5]. The whole loss of hepatic function can cause death in a matter of minutes, highlighting the liver's vital role [6]. Moreover, 50% of acute hepatic failures and 5% of hospital admissions are attributable to drug-induced liver injury [7]. Plasma protein binding, hepatic enzyme capacity, and hepatic blood flow all contribute to how well the liver removes drugs from the body. However, a drug can avoid hepatic clearance through the creation of portosystemic shunts, which are impacted by cirrhosis and, in turn, can also disrupt all these processes [8, 9]. Additionally, many medications' metabolisms and effects are modified by advanced liver disease and cirrhosis through a range of processes, including altered pharmacokinetic behaviour, altered accumulation of free drugs in plasma, and altered end-organ response [10]. The rapid and efficient action of ketoprofen (KP) makes it one of the greatest extensively used non-steroidal anti-inflammatory drugs (NSAIDs) [11]. Specifically, it is extensively employed in the treatment of pain, fever, and inflammatory and musculoskeletal disorders such as rheumatoid arthritis, juvenile idiopathic arthritis, and ankylosing spondylitis [12]. Moreover, this medication can be taken in small doses to treat mild to moderate non-arthritic pain, while a higher dose (around 300 mg) is necessary to treat severe pain associated with arthritic illnesses [13]. However, despite being a powerful analgesic and anti-inflammatory (AF), its use is restricted due to serious side effects and toxicity, most notably stomach exasperation [14], liver injury, and other hepatic disorders [15]. Moreover, KP is an NSAID that is a class of propionic acid and possesses analgesic, AF, as well as antipyretic properties [16]. These medications work by non-selectively suppressing the two cyclooxygenase isoforms (COX-1 and COX-2). However, the harmful effects associated with COX-1 include hepatopathies, nephrotoxicity, altered gastrointestinal function, and coagulation problems [17, 18]. On the other hand, COX-2 inhibition provides therapeutic benefits for

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NSAIDs [19, 20]. Because therapeutic plants contain valuable mechanisms, people have been using them for centuries to extravagance numerous diseases in individuals. The efficacy, affordability, and accessibility of herbal medicines make them an attractive alternative to conventional medicine for treating a wide range of illnesses. This trend has been observed in industrialized and developing nations [21]. So, when drugs are metabolized, an excess of ROS is produced, where ROS attacks protein and targets lipid and nucleic acid macromolecules, causing significant cellular damage [22]. This damage, in turn, significantly contributes to the development and occurrence of liver injury [23]. Artificial antioxidants have been presented in certain culinary applications to scavenge ROS. However, due to potential health risks associated with synthetic antioxidants, including liver damage and carcinogenesis, they have been prohibited [24]. Consequently, the focus has shifted toward natural compounds, which present minimal toxicity and possess promising biological properties as alternative treatments for liver injury, particularly since no effective medicine is currently available [25]. For over 2,000 years, *Ganoderma lucidum* (GL) has been utilized as a medicinal and culinary fungus in China. It is effective in clinical and preventive treatments for various illnesses [26]. Moreover, the accumulation of research has shown that among the bioactive ingredients, such as polysaccharides (PSD), nucleosides, triterpenes, trace elements, alkaloids, and amino acids, *G. lucidum* PSD are the most plentiful materials and have crucial roles in preserving the bioactivities. The current study has concentrated on identifying several bioactive chemicals hidden within *G. lucidum's* fruiting body as the intersection of contemporary science and traditional knowledge becomes more apparent [27]. This finding aligns with advancements in separation and purification technology [28, 29, 30]. Therefore, the current study examined the impact of KP, GL, and their combined effects on liver function through the assessment of many biochemical indicators [aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin (TB)].

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Materials and methods

Drugs

1- GL is manufactured by DXN Pharmaceutical SDN.BHD (was purchased from Malaysia), the bottle contains 70g of Reishi mushroom powder.

2- KP manufactured by European Egyptian pharmaceutical industries (was purchased from a local pharmacy), each capsule containing 50mg of the KP powder.

Animals and housing

Twenty-eight adult male albino rats weighing between 180 and 200 g at 10 weeks of age were utilized. Animals were acquired from the University of Omar Al-Mokhtar's animal house in the Zoology Department of the Science Faculty, El-Beyda, Libya. They were housed in cages at (22 ± 2 °C) following three weeks of acclimatization, as is typical in laboratories. Regular rat food and unrestricted water were provided to the animals. This work complied with all applicable criteria regarding the care and use of laboratory animals, including protocols and procedures.

Ethical Approval

The Al-Mukhtar Bioethics Committee, the Libyan National Committee for Biosafety and Bioethics, the Libyan Authority for Scientific Research, and the University of Omar Al-Mukhtar in El-Beyda, Libya, all gave their approval to the animal trials. A. 24. 16. 007. NBC.

Experimental technique

The following four groups of seven rats each were randomly assigned to comprise twenty-eight rats:

Group (1): The control group was kept under standard laboratory conditions.

Group (2): The GL group (GL), based on Hossain *et al*. [31], animals have been gavaged a dose of (300 mg/kg BW) GL, every day for 4 weeks.

Group (3): In the KP group (KP) under Fadhil and Jebur [32], animals were orally administered with KP (50 mg/kg BW) daily for 2 weeks.

Group (4): The therapeutic group (KP + GL), animals received KP at a dosage of 50mg/kg BW by oral gavage every day for 2 weeks. After two weeks of KP dosing, the animal was given GL at a dose of 300mg/kg BW by oral gavage every day for 4 weeks.

Following the study's conclusion, the blood samples were taken for biochemical examination in dry, clean tubes.

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Chemical analysis of serum

After collecting blood samples and allowing them to clot, the samples were centrifuged for 10 minutes at 3000 rpm and then stored at -80 °C until biochemical analysis was performed. The analyses included measurements of AST, ALP, ALT, and TB, which were conducted on the sera to assess liver enzymatic activity. The AST and ALT were examined according to the method of [33], the ALP was determined according to [34], and the TB was evaluated by Walters and Gerarde [35].

Statistics

The difference between means was ascertained using one-way analysis of variance (ANOVA). The means were separated at $P < 0.05$ using Tukey's test. Two means were also compared using the Paired T-test. Statistical software packages Minitab version 17 and Excel are used for all the data. The information is displayed for each row as the mean ± SE. Differences in superscripts (A, B & C) between the means designate important alterations ($P< 0.05$), whereas identical letter means do not suggest any important alterations ($P< 0.05$).

Results

Investigation of the AST

Results recorded in Table 1 show that compared to the control rats (35.6 ± 1.36), there was a highly significant reduction ($P < 0.05$) in the mean AST level in the GL group (24.6 ± 1.98). In contrast, the KP group presented no remarkable changes in the mean AST level (39.6 ± 2.50), while the KP + GL group exhibited no marked differences in the mean AST level (31.2 ±1.71) compared to the control rats. The combined intake of the KP group and the GL group lowered the AST level compared to the KP group.

Investigation of the ALT

The mean ALT levels for the control and experimental groups are shown in Table 1. No noteworthy differences in ALT activity were observed between the control group (88.8 ± 2.51) and the GL group (88.6 ± 4.29). However, there was an important increase ($P < 0.05$) in ALT activity in the KP group (141.8 ± 9.51) and the KP + GL group (118 ± 8.64) compared with the control group.

Investigation of the ALP

Data for alkaline phosphatase (ALP) levels are presented in Table 1. The average ALP values showed a non-significant difference in the GL group (203.8 ± 10.52) and no important changes in the KP group (251.2 ± 31.90) in comparison to the control group (231.4 ±

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8.02). Additionally, a non-significant ALP level was observed in the KP + GL groups (222.6 ± 6.02) compared to the control group.

Investigation of the TB

Based on the data presented in Table 1, the mean TB values showed no important differences between the treated groups and the normal group. The control group recorded (0.48 ± 0.03), whereas the GL group had (0.54 ± 0.09), the KP group (0.52 ± 0.05), and the KP + GL group (0.5 ± 0.04).

Table 1. ALT, AST, ALP, and TB level averages in the experimental groups.

Parameters	Experimental groups Mean ± SEM			
	Control	GL	KP	KP + GL
AST (U/L)	35.6 ± 1.36 ^{AB}	24.6 ± 1.98 ^{C}	39.6 ± 2.50 ^{A}	31.2 ± 1.71 ^{BC}
ALT (U/L)	88.8 ± 2.51^{B}	88.6 ± 4.29 ^{B}	141.8 ± 9.51^{A}	118 ± 8.64 ^{A}
ALP (U/L)	231.4 ± 8.02 ^{A}	203.8 ± 10.52 ^{A}	251.2 ± 31.90 ^{A}	222.6 ± 6.02 ^{A}
TB (mg/dL)	0.48 ± 0.03 ^{A}	0.54 ± 0.09 ^{A}	0.52 ± 0.05 ^{A}	0.5 ± 0.04 ^{A}

Discussion

In clinical medicine, KP is one of the most widely used NSAIDs with a chiral structure, used as an antipyretic and to treat pain and inflammation [36]. However, along with its numerous beneficial effects, KP can also cause adverse effects such as anaemia, intestinal or stomach ulcers, and blood loss. Moreover, NSAIDs are among the most common causes of drug-induced liver damage [8]. Notably, individuals who take KP on a long-term basis are approximately three times more likely than nonusers to experience severe gastrointestinal complications [37]. Thus, the current investigation was conducted to ascertain the effectiveness of GL in mitigating the physiological alterations in liver tissues induced by KP in male albino rats. This study indicates that, in comparison to the control group, KP treatment increased the activity of live enzymes, including AST and ALT levels. These enzymes are typically situated in the cytoplasm, mitochondria, or both. When a cellular function is changed, injured, or disrupted, these enzymes leak into the bloodstream [38, 39]. El-Feky *et al.* [40] demonstrated how OS and cell membrane damage caused by KP lead to excess free radicals (FR). These FR damage the surrounding tissues and liver cells, leading to liver inflammation and raised levels of hepatic enzymes such as ALT and AST. Additionally, [41] discovered that the liver of birds experiences stress and injury when exposed to

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hazardous doses of KP. This injury can lead to an increase in liver enzyme levels, which are typically found within hepatocytes and play a role in various metabolic activities. However, the enzymes escape into the bloodstream and cause high serum levels when liver cells are killed or injured by OS or direct toxicity from KP. According to [42], KP's high serum ALP and AST readings are suggestive of hepatic abnormalities. Similarly, AST and ALT levels increased when KP was administered a dose of 71.95 mg/kg IP [43]. The most sensitive markers are ALT and AST, which react rapidly to changes in liver cells [44, 45]. Furthermore, because ALT is mostly found in the liver as a cytosolic protein and in trace amounts elsewhere, it is believed to be more specific for hepatic injury than AST [46]. According to [47, 48], KP has also been linked to a range of hepatic adverse effects, from fulminant hepatic failure and hepatotoxicity to symptomless increases in aminotransferase levels and hepatitis with bitterness. Moreover, diseases like cirrhosis, cancer, viral or toxic hepatitis, medication responses, and bile duct obstruction that cause some degree of liver cell destruction are frequently the source of elevated liver enzyme levels [49, 50]. Additionally, treatment for different forms of NSAIDs results in a noticeable rise in ALP, TB, AST, and ALT [51]. Furthermore, [52] presented contrary results, stating that there was no discernible alteration in serum TB, ALT, and AST levels between NSAID-treated animals and normal animals. Meanwhile, GL causes ALT, ALP, and AST levels to fall, but there is no discernible difference in TB levels as compared to control animals. The findings conflict with [53] and [54], who found that the rats treated with GL alone have reduced hepatic enzyme activity. In the present investigation, KP was used to induce hepatic injury to examine the effectiveness of GL. Serum levels of ALT, AST, and ALP were measured to examine the impact of the GL diet on the structural integrity of the liver. Oral administration of KP led to a noteworthy rise in plasma levels of ALT and AST, along with a non-marked rise in ALP and TB. In contrast, treatment with GL significantly reduced these enzyme levels in the KP + GL group of rats. Similar findings have been reported in previous studies [55, 56]. Increases in these enzymes signify improper membrane permeability or hepatocyte necrosis, whereas decreases show that the hepatic parenchyma has healed [57]. Moreover, GL showed antioxidative and AF properties in the earlier laboratory findings [58]. Many recent studies have shown how effective GL is at scavenging FR, which significantly

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slows the progression of inflammation and OS. Therefore, GL may be utilized as a treatment for hepatic damage brought on by hepatotoxic materials [59, 60]. Furthermore, the GL contains ingredients such as flavonoids, steroids, and Ling-Zhi 8, where flavonoids show strong inhibitory activity against several enzymes, such as kinase C, tyrosine kinase, phospholipase A2, and phosphodiesterase [61]. On the other hand, *Ganoderma* contains ergothioneine, an amino acid that comes from thiourea and histidine derivatives with sulfur atoms in the imidazole ring. It is used as a protein source to help with liver impairment and to activate the glutathione S-Transferase enzyme as a detoxification enzyme. It also has anti-inflammatory properties, primarily through the triterpene group, which inhibits the production of proinflammatory mediators like PGE2, TNFα, and IL-6 [62]. Also, Liu *et al.* [63] said rats' acute liver damage is avoided because GL efficiently lowers inflammation and liver dysfunction.

Conclusion

This work presented that GL aqueous extract had hepatotherapeutic potential against hepatic damage caused by KP in male albino rats. Significant biochemical changes, such as increased liver enzyme levels, were brought on by the administration of KP. However, GL treatment led to a notable decrease in enzyme levels, indicating that it is effective in treating KP-induced liver damage. The results demonstrate GL's AF and antioxidant qualities as a natural remedy for preventing drug-induced liver damage. To clarify its underlying molecular mechanisms and improve dosing techniques for therapeutic application, more research is required**.**

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