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MOLECULAR DOCKING OF BERBERINE TO REDUCE OSTEOARTHRITIS INDUCED BY HYDROXYZINE IN MALE RABBITS

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ABSTRACT

Berberine (BBR) has been prescribed in the management of various health conditions, and its potential as a powerful natural remedy continues to attract scientific interest in the treatment of inflammatory disease. This study involved twenty-four male rabbits, which were randomly divided into four equal groups, each consisting of six rabbits. The first group served as the negative control, while the second group was the positive control, in which arthritis was induced using hydroxyzine. The third group included rabbits with induced arthritis and treated with berberine, and the fourth group consisted of rabbits with induced arthritis and treated with leflunomide. The molecular study results demonstrated that celecoxib exhibited a highly comparable binding affinity with the receptor, when compared to berberine and its active components. Additionally, it showed significant efficacy in inhibiting cyclooxygenase-2 (COX-2), contributing to the reduction of joint inflammation and associated pain. These findings suggest its potential as a future natural therapeutic option, which may help minimize the side effects associated with conventional chemical treatments. The study found that berberine effectively reduced rheumatoid factor levels and C-reactive protein, indicating its potential as a therapeutic agent for RA.

Keywords: C-reactive protein , Arthritis, cyclooxygenase-2, berberine (BBR)

INTRODUCTION

Rheumatoid arthritis is defined as a group of conditions characterized by joint inflammation, leading to signs such as pain, stiffness, swelling, and difficult mobility.

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Qasim *et al.* (2021) reported that the berberine mode of action underlying this autoimmune defect is still unclear. In spite of that, multiple key factors elaborated in the rheumatoid arthritis (RA) pathogenesis have been determined. Cyclooxygenase enzymes are central to the body's inflammation process, as they help activate immune cells and promote the release of

signaling proteins that drive inflammation. Additionally, cytokines such as TNF-α, IL-1β, IL-6, and NF-Kβ participate significantly in the progression and prognosis of RA (Jenkins *et al.,* 2022). The main strategies for RA comprise NSAIDs, disease-modifying antirheumatic drugs, and novel biologics such as TNF monoclonal antibodies and IL-1 receptor blockers. Despite advancements in RA treatment strategies, research is going on to discover new therapeutic options capable of preventing long-term joint damage and functional disability. In addition, side effects associated with available treatment options and their high cost are another reason for finding an alternative antiarthritic agent with low side effects and less cost. Joint dysfunction due to chronic inflammation and severe pain are hallmarks of RA (Figure 1). Thereby, drugs with anti-inflammatory and analgesic potential act as antiarthritic agents (Schrieber, 2014).

Berberine (BBR) is a natural compound extracted from several plants, including the barberry shrub. Berberine, traditionally utilized in Chinese and Ayurvedic medicine, has garnered attention for its potential health benefits (Sun et al., 2019). BBR has a wide range of medical applications in both humans and animals, including the treatment of Alzheimer's disease, obesity, gastroenteritis, chronic diarrhoea, malaria, polycystic ovary syndrome (PCOS), diabetes, and hypotension (Habtemariam, 2020). In both in vitro and clinical studies, BBR has demonstrated minimal toxicity in humans (Alnuqaydan *et al.,* 2022). Although BBR exhibits significant in vitro antibacterial activity against various pathogenic organisms, including fungi, protozoa, trypanosomes, and plasmodia, its effectiveness against *Escherichia coli* (*E. coli*) strains causing diarrhea in chicken chicks remains underexplored (Imenshahidi and Hosseinzadeh, 2019).

Nazir *et al.* (2024) indicated that berberine possesses anti-inflammatory and antioxidant properties, which may be beneficial in managing conditions like arthritis. Some studies suggest that berberine can modulate the body's inflammatory responses and reduce oxidative stress, potentially alleviating joint inflammation and pain associated with arthritis (Figure 2) (Yu *et al.,* 2024, Wang *et al.,* 2023, Shakeri *et al.,* 2024). While these findings are promising, to confirm the clinical value of berberine's efficacy and safety in arthritis treatment. Arthritis encompasses a range of joint disorders that can impair quality of life, and berberine is a plant-derived compound under investigation for its potential therapeutic effects on inflammatory conditions such as arthritis (Asbaghi *et al.,* 2020, Neamah *et al.,* 2024). Molecular docking of the current study has been done to explain the molecular interaction between berberine and COX-2, the latter an enzyme associated with inflammatory processes. These projects aimed to predict how berberine binds to COX-2 at the molecular level, delivering insights into its potential as an anti-inflammatory agent (Alnuqaydan *et al.,* 2022; Yu *et al.,* 2024; Jabber *et al.,* 2022). A particular study showed that berberine binds tightly to the COX-2 enzyme, indicating a suitable interaction (Taidi *et al.,* 2022). These molecular docking studies, along with experimental evidence, suggest that berberine's interaction with COX-2 is a key factor in its anti-inflammatory activity (Wang *et al.,* 2024). This study aims to explore the molecular docking interactions of the active compounds of berberine with COX-1 and COX-2 enzymes, using docking analysis, and to benchmark these interactions against celecoxib. Additionally, the study aims to evaluate the therapeutic efficacy of berberine in reducing experimentally induced rheumatoid arthritis in rabbits.

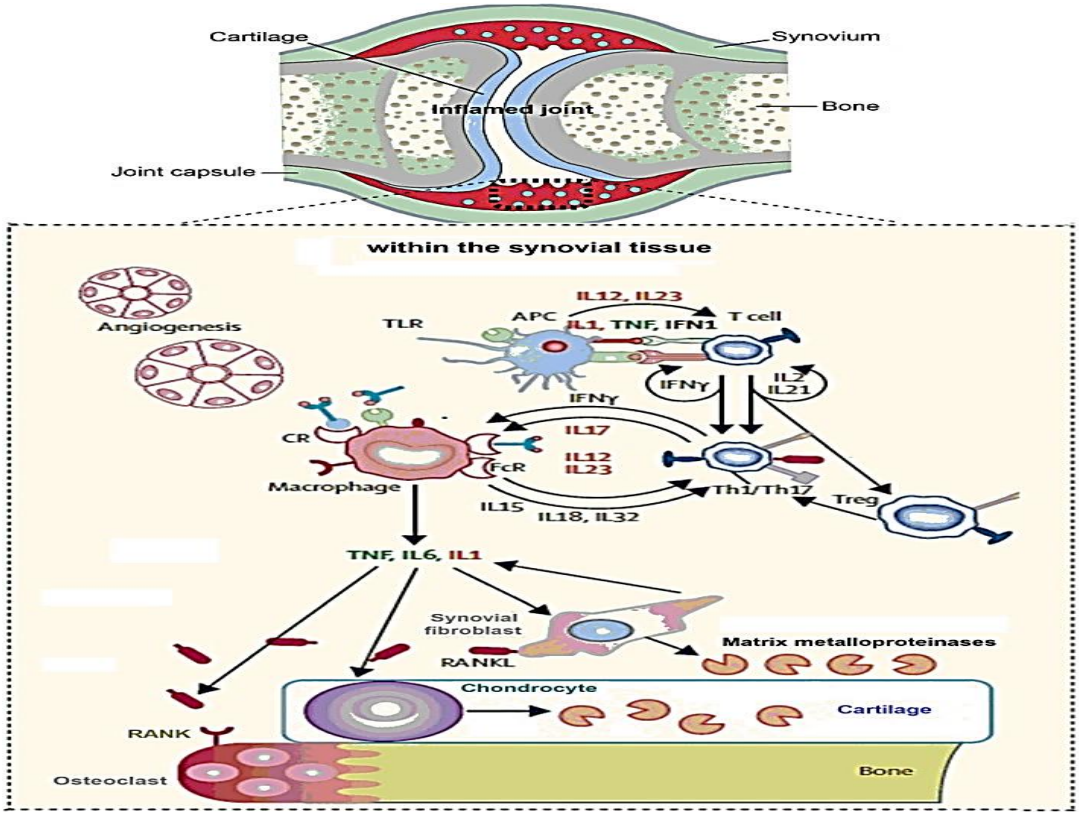

Fig. 1: Pathogenesis of arthritis inflammatory cytokines (Ji and Hong, 2019)

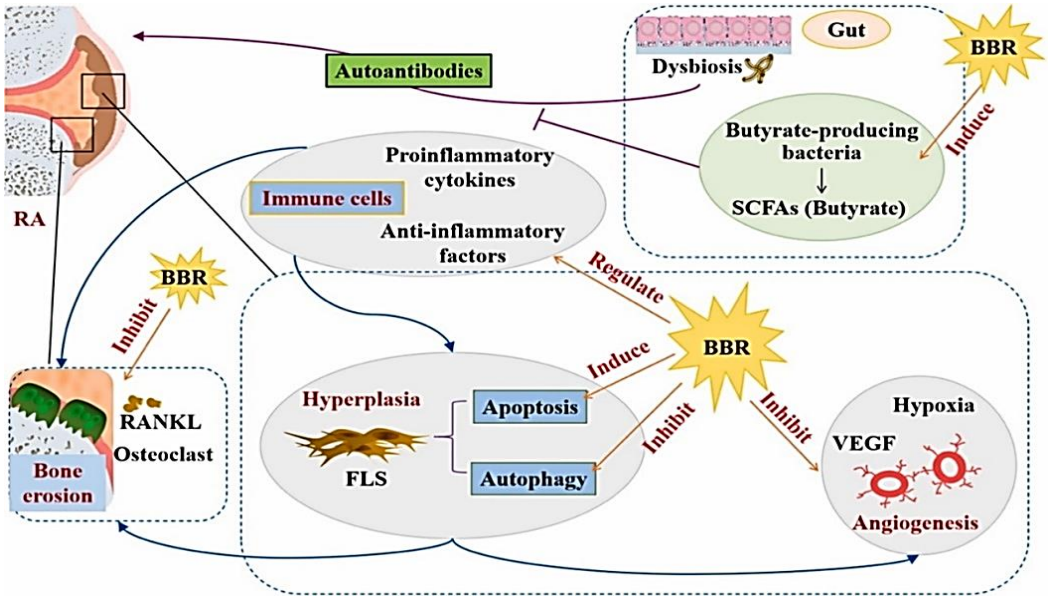

Fig. 2: Mechanism of action of berberine in the treatment of arthritis (Ji and Hong, 2019)

MATERIALS AND METHODS

Chemical:

Berberine was obtained from a company in the USA, and hydroxyzine was obtained from Pfizer.

Animals

A total of twenty-four male albino rabbits, aged between 15 and 20 weeks and weighing 1.2–1.4 kg, were procured from a local animal house for this study. Prior to

beginning the experimental study, all animals received a prophylactic treatment with ivermectin and enrofloxacin. The rabbits were then randomly assigned into four groups, each consisting of six animals. The rabbits in the current study were maintained on a standard diet and provided with tap water daily throughout the experiment. To induce experimental arthritis in all groups except the negative control, hydroxyzine was administered to eighteen rabbits at a dose of 8 mg/kg orally for a duration of two months, as described by Rubin *et al.* (2020), and the induction was confirmed according to clinical symptoms, serum RF, and the selection of three rabbits randomly for histopathological section. Following this induction period, the arthritic rabbits were divided into three treatment groups: one group received no further intervention (the arthritic untreated group), the second group was treated with berberine at a dose of 100 mg/kg, and the third group received leflunomide at a dose of 1 mg/kg. Both treatments were continued for six weeks. Blood samples were collected via the marginal ear vein for biochemical analysis and were stored at −20°C until further examination.

Molecular Docking

Molegro Virtual Docker 2019 7.0.0 (MVD, a full trial version) was used to perform the docking studies. The crystal structures of the template proteins, PDB ID 5JW1 and PDB ID 8ET0, were downloaded from the Protein Data Bank (Eliwa *et al.,* 2022).

Statistical analysis

The evaluations were conducted using one-way analysis of variance (ANOVA) and subsequently subjected to Dunnett's post hoc test for multiple comparisons, implemented via GraphPad Prism software (version 5.0). Results were presented as mean ± standard error of the mean (SEM). Statistical significance thresholds were defined as $P<0.05$ (Neamah *et al.,* 2024).

RESULT

Molecular study

As of now, there is no specific data available regarding the binding affinity between berberine and the protein structure identified by PDB ID 8ET0. This particular protein structure has not been widely studied in the context of berberine interaction. However, berberine has been shown to exhibit binding affinities of -8.6 kcal/mol with COX-1 and -9.0 kcal/mol with COX-2 enzymes. Additionally, berberine has been reported to bind to human telomeric quadruplex DNA with a binding constant of approximately 1.2 × 10^6 M^-1, corresponding to a free energy change (ΔG) of -8.2 kcal/mol.

Table 1: Molecular Docking Results and Potential Effects.

Compound	Binding Affinity (kcal/mol)	Key Interactions	Potential Effect on COX-2
berberine	-8.6	Hydrogen bonds with active site residues	Inhibits TNF-α and IL-6, reducing inflammation
Palmatine	-8.2	Hydrogen bonds with active site residues	Inhibits TNF-α and IL-6, reducing inflammation
Columbamine	-7.8	Hydrophobic and electrostatic interactions	Reduces oxidative stress and joint damage
Jatrorrhizine	-8.5	π-π stacking and hydrogen bonding	Analgesic and anti-inflammatory properties
Celecoxib (Reference Drug)	-9.0	Strong hydrophobic interactions with COX-2	Selective COX-2 inhibition, reducing pain and inflammation

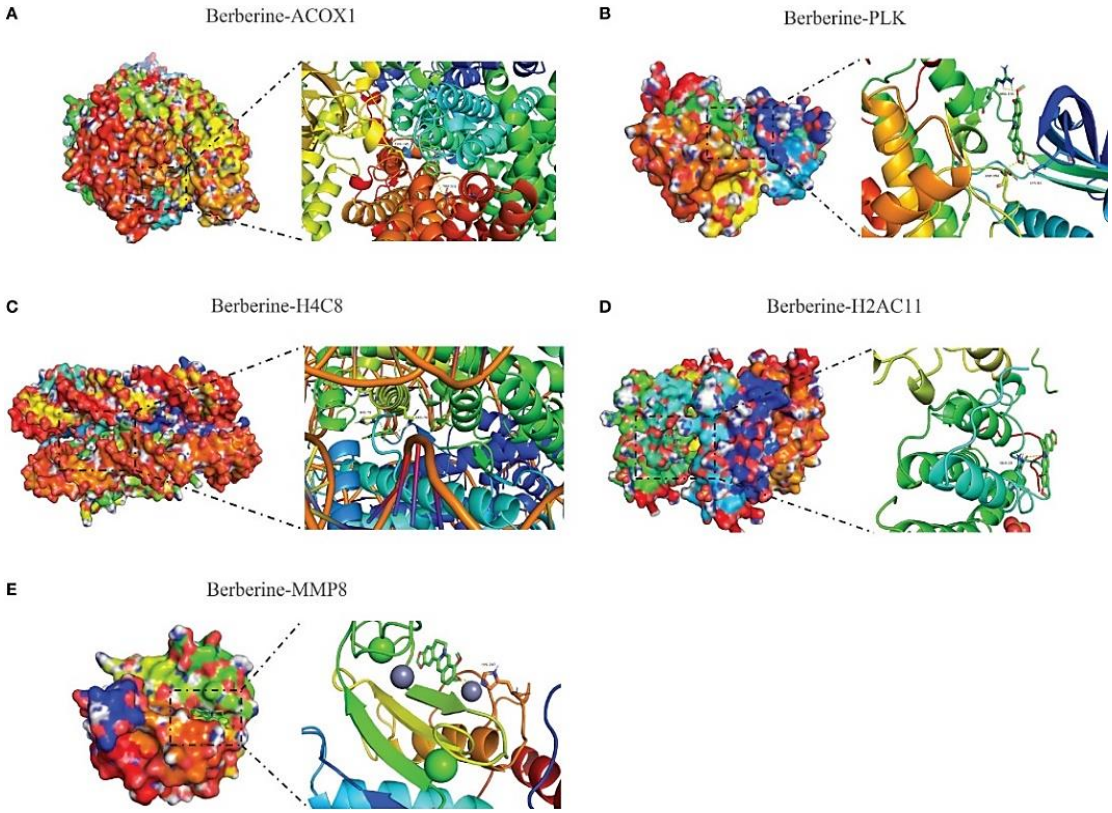

Fig. 3: The protein structure identified by PDB ID 5JW1 corresponds to the human cyclooxygenase-2 (COX-2) enzyme. Berberine, a natural isoquinoline alkaloid, has been studied for its interaction with COX-2. In molecular docking studies, berberine demonstrated a binding energy of -8.6 kcal/mol with COX-1 and -9.0 kcal/mol with COX-2, suggesting a higher affinity for COX-2. These interactions were primarily stabilized by hydrogen bonds and hydrophobic interactions within the active site of the enzyme.

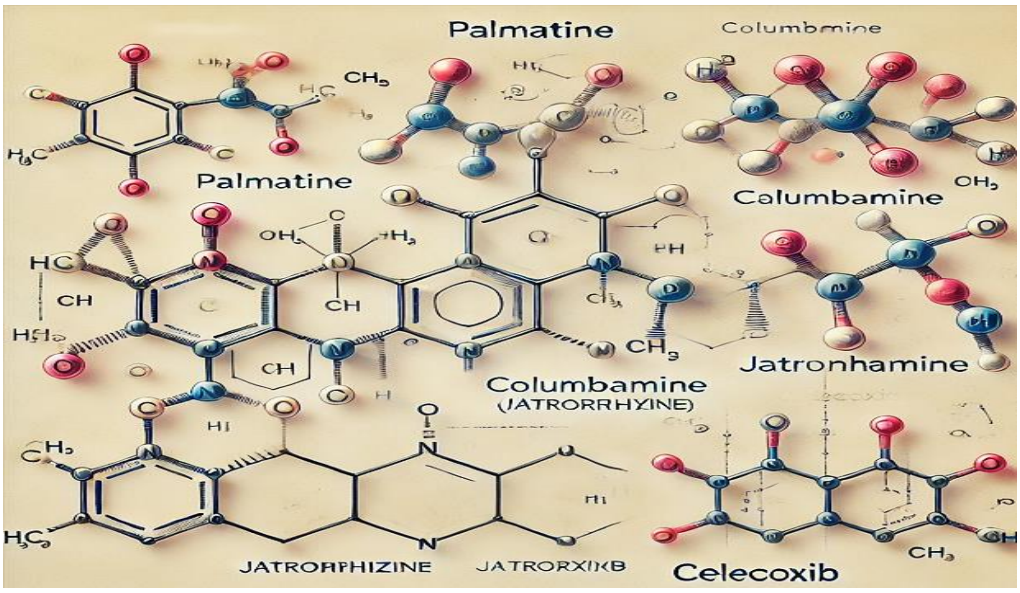

Fig. 4: The structure diagram depicts Palmatine together with Columbamine, Jatrorrhizine and Celecoxib through their molecular bonds and functional groups understanding. These compounds are active on the COX-2 enzyme, which enables their anti-inflammatory mechanism. The displayed chemical structures illustrate how these compounds match Celecoxib regarding their role as COX-2 inhibitors.

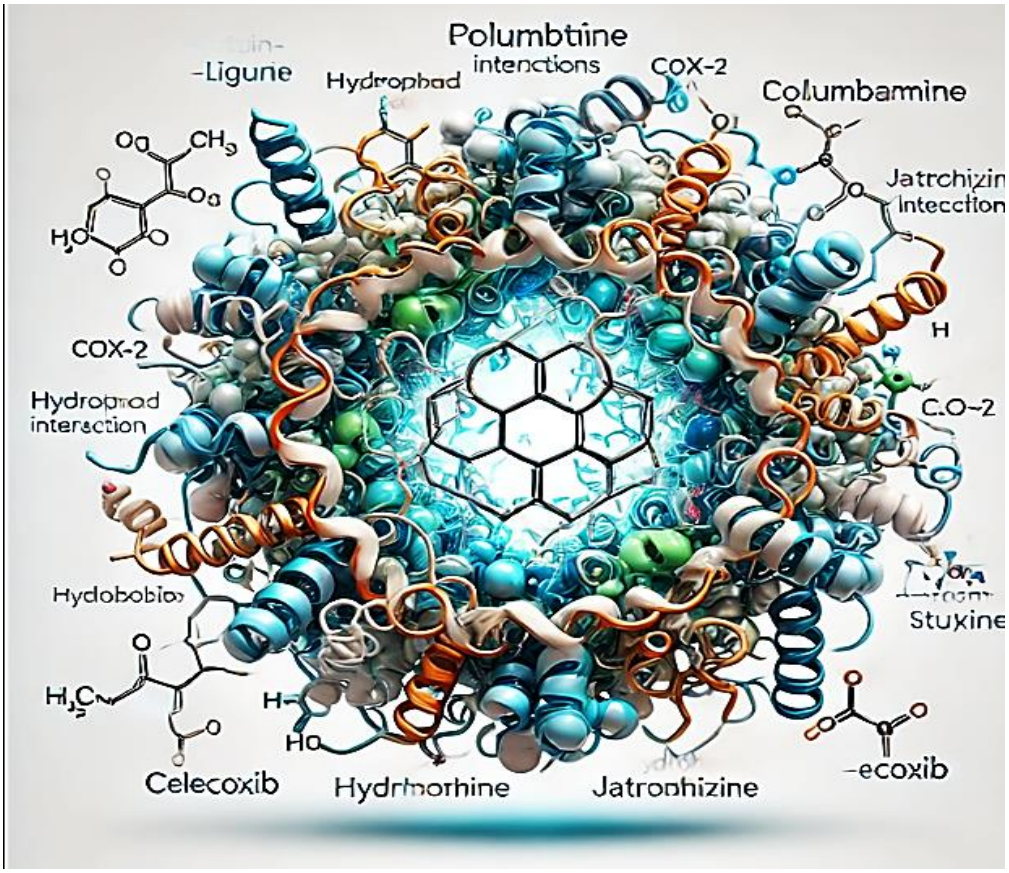

Fig. 5: The binding relationships among Palmatine and Columbamine and Jatrorrhizine compounds with COX-2 are shown with reference inhibitor Celecoxib in this illustration. The illustration shows various bonding interactions, which involve hydrogen bonds along with hydrophobic contacts and π-π stacking systems to explain their possible influence on COX-2 inhibition and anti-inflammatory properties.

The COX-2 enzyme docking outcome reveals substantial substrate interactions between all three natural alkaloids, palmatine, columbamine, and jatrorrhizine, although with varying strengths of chemical bonds.

The binding affinity of palmatine to the active site reaches -8.2 kcal/mol through hydrogen bonding with active site residues. The natural alkaloids demonstrate the capacity to block pro-inflammatory proteins, such as TNF-α and IL-6, which indicates their potential anti-inflammatory properties.

Hydrophobic alongside electrostatic interactions drive the binding of Columbamine between molecules, which produces a weaker affinity than Palmatine (-7.8 kcal/mol). The therapeutic applications of Columbamine become stronger because it shows a remarkable ability to protect joints from damage and lower oxidative stress levels.

Jatrorrhizine exhibits the second most potent binding affinity within natural alkaloid molecules through interactions of both π-π stacking and hydrogen bonding (-8.5 kcal/mol). The combination of analgesic and anti-inflammatory actions turns it into an attractive future therapeutic agent.

The selective COX-2 inhibitor celecoxib demonstrates its strongest binding affinity of -9.0 kcal/mol, which stems mainly from powerful hydrophobic forces. The strong binding affinity supports the effectiveness of this drug as an anti-inflammatory

benchmark agent. All alkaloids show binding affinity, but celecoxib functions as the most potent inhibitor. Jatrorrhizine shows a binding affinity that matches closely enough with cyclooxygenase enzymes to indicate its worth for treatment purposes. The active site of COX-2 accepts binding contributions from three different interaction types, which include hydrogen bonding as well as electrostatic forces and π-π stacking. These natural alkaloids exhibit anti-inflammatory properties, which could potentially fill the role of alternative or additional COX-2 inhibitors during in vitro and in vivo research.

Biochemical evaluation

The present study found that the serum concentration of C-reactive protein (CRP), an inflammatory marker, was significantly elevated in rabbits exposed to hydralazine, which served as a positive control, compared to both the negative control group and rabbits treated with leflunomide; furthermore, CRP levels were significantly reduced after administering berberine extract orally to the rabbits (Fig. 6).

The NCG group in Fig. (7) exhibits the lowest RF concentration as compared with positive control rabbits exposed only to hydralazine.

The findings indicate that rabbits in the third group, which received Berberine plus HHC, show in Fig. (7) a clear and significant reduction of ALP. The findings of the present study indicate that leflunamide has a role in reducing ALP enzyme and TNF-α levels in rabbits with induced arthritis through hydrazine administration. The current study noted that berberine has a significant reduction of TNF-α as compared with the positive control group, as well as that there was no significant difference when compared with leflunomide.

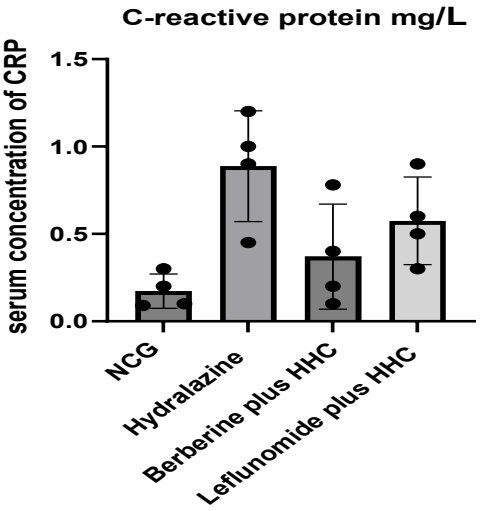

Fig. 5. Effect of berberine and leflunomide on serum CRP in rabbits with induced arthritis.

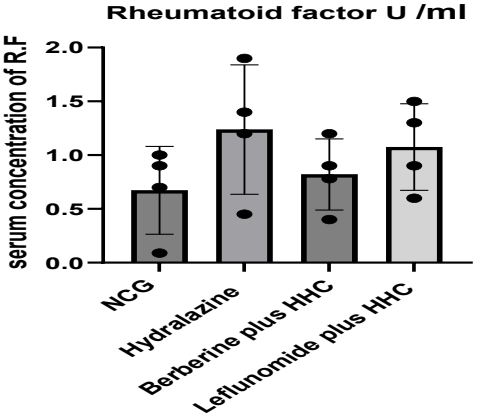

Fig. 6. Effect of berberine and leflunamide on serum RF in rabbits induced arthritis.

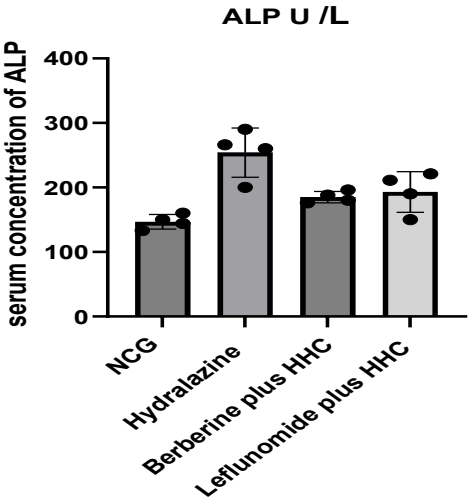

Fig. 7. Effect of berberine and leflunamide on serum ALP in rabbits induced arthritis.

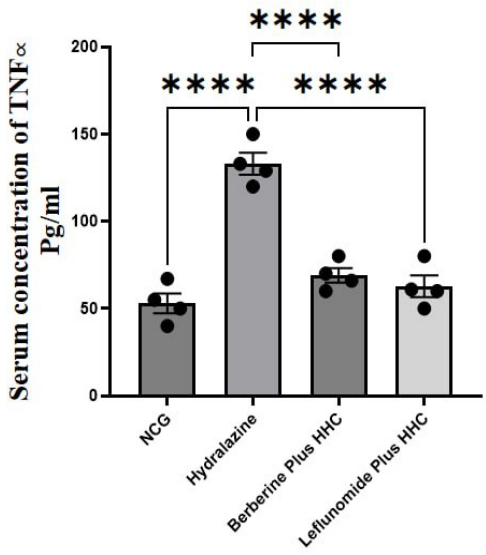

Fig. 8. Effect of berberine and leflunamide on serum TNF-α in rabbits with induced arthritis.

DISCUSSION

The drug docking study of main active compounds in berberine (berberine, palmatine, columbamine, and jatrorrhizine) compared with celecoxib as a reference drug appears to have variant binding affinity to the COX-2 enzyme receptor (-8.6, -8.2, -7.8, -8.5, and -9.0, respectively). In addition to that, natural compounds like berberine and jatrorrhizine show binding affinities close to celecoxib, indicating their potential as alternative or complementary anti-inflammatory agents, especially in cases of NSAID sensitivity.

Pharmacological potential of these compounds: Berberine and palmatine compounds appear to suppress key inflammatory mediators like TNF-α and IL-6, which could make them valuable in reducing immune-driven inflammation (Qin *et al.,* 2024). A recent study by Fatima Hashmi *et al.* (2024) noted that Jatrorrhizine has pain-relieving and anti-inflammatory activity, likely aided by its ability to engage in aromatic stacking and hydrogen bonding within target sites. The results of the current study indicated that administration of hydrazine to rabbits led to noticeable joint inflammation. This inflammation was evident through clinical signs such as difficulty in walking or stiff gait, as well as through biochemical tests, which showed elevated serum levels of CRP, RF, ALP, and TNF-α. The results of the current study demonstrated the role of berberine plant extract in reducing clinical signs and improving the levels of the studied biochemical parameters toward values close to the normal range. This indicates its antioxidant and anti-inflammatory properties, which contribute to decreasing the inflammatory processes that exacerbate the progression of rheumatoid arthritis.

The present study was concordant with Iyer *et al.* (2017): hydralazine is associated with drug-induced lupus erythematosus and drug-induced arthritis, primarily through immune system activation. A lower RF level compared to the hydralazine group, suggesting a possible protective effect. This suggests that berberine could contribute to reducing autoimmune responses and decreasing RF concentration, much like leflunomide. The findings of the present study indicate that berberine has a role in reducing ALP enzyme and TNF-α levels in rabbits with induced arthritis through hydrazine administration. The reduction was statistically significant compared to leflunomide, suggesting that berberine may help slow disease progression and alleviate its symptoms effectively.

The precise mechanism remains incompletely elucidated, yet several principal processes play a contributory role: Altered immune response promotes epi-genetic modifications, autoantibody production, and cytokine activation: Hydralazine increases pro-inflammatory cytokines, such as TNF-α and IL-6, leading to joint inflammation and damage (Handler, 2011; Kumar *et al.,* 2018; Rubin *et al.,* 2020).

Berberine exerts its anti-arthritic properties by reducing C-reactive protein as well as was concordant with confirmed improvement by multiple mechanisms. One of these mechanisms is the inhibition of pro-inflammatory cytokines. Studies indicate that berberine blocks the production of inflammatory cytokines such as TNF-α, IL-6, and IL-1β, which are major contributors to arthritis progression (Nazir *et al.,* 2024). It also inhibits the activation of nuclear factor-kappa B (NF-κB), a key regulator of inflammation involved in joint destruction. Reduction of Oxidative Stress Oxidative stress plays a crucial role in cartilage degradation in arthritis. Berberine has been shown to increase antioxidant enzyme activity while reducing reactive oxygen species (ROS), thus protecting joint tissues (Wang *et al.,* 2024, García-Muñoz *et al.,* 2024).

Berberine's Influence on C-Reactive protein (CRP): CRP is a crucial marker of inflammation and is commonly elevated in arthritis patients. Berberine affects CRP levels through several pathways: Direct lowering of CRP levels. Clinical studies have reported that administered berberine significantly lowers serum CRP levels in individuals with chronic inflammatory conditions, including arthritis (Huang *et al.,* 2021).

Berberine, a natural compound, has apparent potential therapeutic value for arthritis by reducing rheumatoid factor (RF), alkaline phosphatase (ALP), and TNFα. Effect on ALP serum levels: raised ALP is often related to bone and joint defects such as arthritis. Naz *et al.* (2022) confirmed that berberine has antioxidant and anti-inflammatory properties that may help regulate bone metabolism. By regulating osteoblast and osteoclast function, it may also protect against the degradation of bone associated with arthritis. Berberine has been found to improve the response of the immune system, potentially reducing RF levels. It blocks key inflammatory pathways, including NF-κB, TNF-α, and IL-6, which play a crucial role in autoimmune conditions.

CONCLUSION

The present study showed that berberine has the ability to inhibit cyclooxygenase-2 (COX-2), contributing to the reduction of joint inflammation and associated pain. These findings suggest its promise as a natural treatment alternative, with the added advantage of potentially reducing the unwanted effects linked to traditional drug therapies.

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الالتحام الجزيئي لمادة البربرين في الحد من التهاب المفاصل التنكسي المستحث بواسطة الهيدروكسيزين في ذكور الأرانب

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-[3]كلية الطب البيطري، جامعة القاسم الخضراء، بابل ٥٠١٣، العراق.
-[4]قسم تقنيات التخدير، جامعة الزهراء، العراق.

يُوصف البربرين لعلاج العديد من الحالات الصحية، ولا يزال استخدامه كعلاج طبيعي فعال يجذب اهتمامًا علميًا في علاج الأمراض الالتهابية. شملت هذه الدراسة أربعة وعشرين أرنبًا ذكرًا، قُسِّمت عشوائيًا إلى أربع مجموعات متساوية، تضم كل منها ستة أرانب. ضمت المجموعة الأولى مجموعة التحكم السلبية، بينما ضمت المجموعة الثانية مجموعة التحكم الإيجابية، حيث تم تحفيز التهاب المفاصل باستخدام هيدروكسيزين. ضمّت المجموعة الثالثة أرانب مصابة بالتهاب المفاصل المُستحثّ وعولجت بالبربرين، بينما ضمّت المجموعة الرابعة أرانب مصابة بالتهاب المفاصل المُستحثّ وعولجت بالليفلونوميد. أظهرت نتائج الدراسة الجزيئية أن السيليكوكسيب أظهر ألفة ارتباط عالية التقارب مع مستقبلات السايكلواوكسجينيز، مقارنةً بالبربرين ومكوناته النشطة. بالإضافة إلى ذلك، أظهر فعالية كبيرة في تثبيط إنزيم سيكلوأكسجيناز-٢، مما ساهم في تقليل التهاب المفاصل والألم المصاحب له. تشير هذه النتائج إلى امكانيه استخدام المثبطات الطبيعية للانزيم كعلاج طبيعي مستقبلي، مما قد يساعد في تقليل الآثار الجانبية المرتبطة بالعلاجات الكيميائية التقليدية. توصلت الدراسة إلى أن البربرين يقلل بشكل فعال من مستويات البرو عامل الروماتويد والبروتين التفاعلي، مما يشير إلى إمكانية استعماله في علاج التهاب المفاصل الروماتيدي.

الكلمات المفتاحية: البربرين , التهاب المفاصل التنكسي , ذكور الأرانب