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The Role of Propolis in Muscle Repair: A Systematic Review

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ABSTRACT

Propolis a natural substance that comes from bees possesses various medicinal properties including. antioxidant, anti-inflammatory, and beneficial in the metabolic system. Muscle repair is crucial for maintaining muscle function, especially in cases of injury, oxidative stress, and ageing which cause muscle loss and dysfunction. Propolis has emerged as a potential alternative treatment for muscle repair. **Objective:** To investigate the impact of propolis on muscle repair. **Methods:** A systematic literature review was conducted using databases such as PubMed, Google Scholar, Research Gate, and Cochrane Library. The PRISMA guideline was followed for analysis. The approach uses keywords such as propolis, muscle, and skeletal muscle. Articles were selected based on sample characteristics, intervention, and muscle repair parameters. The searched keywords include propolis, muscle, and skeletal muscle. Evaluation parameters included oxidative stress markers, inflammation, molecular mechanisms, muscle capillaries, muscle mass, strength, and function. **Results:** The initial search uncovered 7676 articles, after further screening, it comprised a total of 21 studies that were included in the results. The collected articles summarized the main mechanism of action of propolis in muscle repair, primarily due to its antioxidant, and anti-inflammatory properties, and its effect on glucose metabolism, which influences muscle fatigue, strength, and mass. **Conclusions:** It was concluded that propolis as a bee's natural product, has several advantages in muscle repair due to its multiple mechanisms of action, encompassing antioxidants, anti-inflammatory properties, impact on muscle glucose metabolism, and stimulation angiogenesis.

INTRODUCTION

Muscle damage can result from inflammation caused by stress, trauma, and ageing leading to muscle pain, discomfort, weakness, and impaired function. Skeletal muscles are crucial for mobilization and energy metabolism. Disorders in skeletal muscles can hinder mobility and disrupt energy metabolism. Muscle damage leads to systemic disorders due to important receptors on muscle cells [1]. In addition, muscle damage also causes disorders in the neuromuscular system, causing fatigue and disrupting activities [2]. Diseases that cause muscle damage are numerous and varied. These diseases can originate directly from the muscle or be related to other systems. Some diseases associated with muscle damage are due to metabolic disorders (e.g. diabetes and obesity), hormonal imbalance (e.g. menopause) and nerve damage in sciatic injuries [1, 3]. Approximately 11.4% of diabetics from a population sample in Italy have muscle disorders, conversely, a lack of muscle mass will increase the incidence of type 2 diabetes [4, 5]. Musculoskeletal health problems also occur in 70% of women who experience menopause due to hormonal imbalance, which causes damage to the skeletal muscles [6]. It is not only diseases that cause muscle damage, but excessive activities that induce stress such as training or sports in athletes can also cause muscle damage [7]. In ageing, there is also a condition of muscle weakness and a decrease in quality called sarcopenia [8, 9]. Sarcopenia is also related to other conditions such as menopause, obesity, cardiovascular [9-11] and type 2 diabetes. Muscle repair is influenced by various factors like age, nutrition, physical activity, and overall physical health. Indicators of muscle repair include myoblasts activity, which are muscle progenitor cells that

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play a role in muscle cell repair, and the balance of anti-inflammatory and pro-inflammatory cell activity [12]. A well-functioning circulatory system and capillary network are essential for efficient muscle repair. Muscle mass and strength are key parameters for assessing muscle improvement. Various methods like medication, exercise, physical therapy, and supplementation are used for muscle repair, with a natural supplement like propolis gaining popularity. Propolis also known as bee glue, is a bee product used to protect bee hives and contains active ingredients with antioxidants and anti-inflammatory properties beneficial for muscle damage [3, 12]. So far the role of propolis in muscle repair works largely through its anti-oxidant and anti-inflammatory effects for muscle health. While studies have extensively researched the effects of antioxidants, oxidative stress, and inflammation on repair, few have focused on the direct impacts of propolis on muscle function improvement. Muscle function parameters that are usually assessed are muscle strength and locomotion function [13].

Despite growing evidence on the antioxidant and anti-inflammatory properties of propolis, there is limited high-quality human-based research directly evaluating its effects on muscle repair and functional outcomes. Most existing studies rely on animal models or in vitro findings, with inconsistent results regarding muscle strength and performance in humans. Additionally, variability in propolis composition and dosage limits the generalizability of findings. Therefore, this study aims to systematically evaluate the role of propolis in muscle repair, focusing on its mechanisms, effectiveness, and impact on muscle function, strength, and metabolic regulation.

METHODS

The study followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines established by Page *et al.*, [14]. The patient/population, intervention, comparison and outcomes (PICO) approach was utilized to conduct various databases, such as PubMed, Google Scholar, Research Gate, and the Cochrane Library to identify relevant English-language publications. All the published articles between 2006 to 2023 were selected to conduct this systematic review. Comprehensive search techniques were employed to identify studies meeting the eligibility criteria, which include experimental studies with muscle repair outcomes, accessible articles, full-text articles published in English, and no limitation of publication year. The initial keyword used was "propolis" followed by additional keywords such as “muscle”, “skeletal muscle”, “muscle repair”, “human”, “rodent”, “mice” and “rat” using the AND/OR operator. All selected studies were reviewed based on predefined inclusion and exclusion criteria [13]. This research focused on original experimental studies on animal models, cell cultures, or human populations in muscle damage conditions. The study included an intervention involving propolis administration. Articles that did not meet the specified criteria were excluded. Data collected from eligible articles included sample models, intervention details, and muscle improvement parameters, which are indicators of molecular or functional muscle repair progress. The PRISMA process of article selection is depicted. The initial literature search yielded 7676 articles from various search engines. Among these, 53 articles with duplicate titles were excluded. Upon screening the titles and abstracts, 157 articles were identified for further review. Subsequently, 90 articles were excluded as they did not meet the inclusion criteria or were not closely related to the topic of interest. Out of the remaining 67 articles, 46 were further excluded due to non-English language, incomplete design explanations, or sample and research outcome discrepancies. Finally, 21 articles were included in this literature review based on meeting the desired criteria (Figure 1).

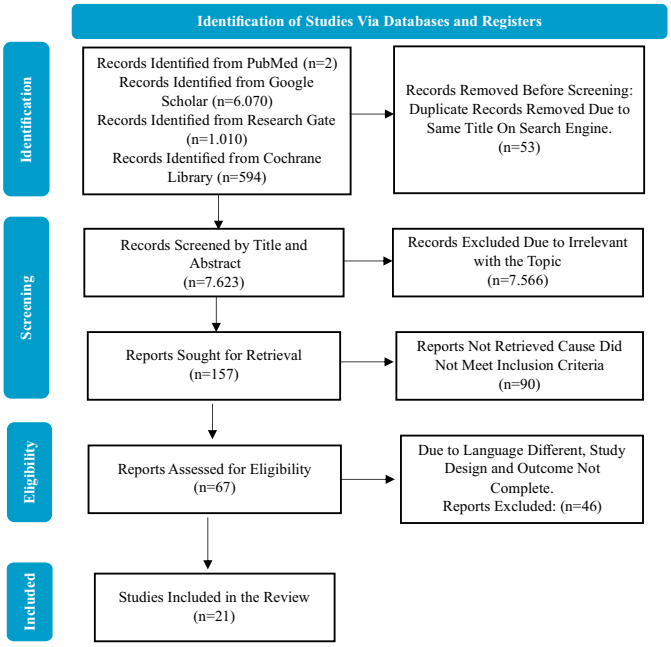

Figure 1: Article Selection Process Following PRISMA Method

RESULTS

The selected articles encompassed research published from 2006 to 2023, involving human subjects, rodents (mice or rats), and in vitro and ex vivo cell cultures. Various interventions were administered to the research subjects to influence muscle conditions, including effects on muscle cells, metabolism, and muscle function. These interventions ranged from systemic interventions like high glucose level, age-related factors, and injury models such as ischemic and nerve injuries impacting muscle function. Additionally, stress induction in muscle was also achieved

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through exercises, chemokine, and compound induction leading to heightened oxidative stress. These interventions typically resulted in increased inflammation and oxidative stress in the muscles. Infection, congenital conditions, and genetic engineering related to muscle damage were excluded from this study. The results of 21 articles related to human subjects were summarized in table 1.

Table 1: The Role of Propolis Intervention in Studies

References	Sample/Population	Sample Induction	Propolis Intervention	Muscle Repair Parameter
Human Subjected				
[15]	Adult Men	Practice 3 Sessions/Week, for 30 Days	Propolis 70 mg/day for 30 Days	Reduce Pain Caused by Intense Exercise Decreases Inflammatory Activity
[16]	Men Military Cadets	The Cooper Test (12 Minutes of Running and Sprinting Based On Anaerobic Test Results)	Single Dose of 450 mg Propolis, 2 Times/Day for 4 Weeks	Reduces Oxidative Stress Index Increases Antioxidant Activity Reduces Pro-Inflammatory Activity. No Significant Impact On Fatigue Index
[17]	Young Adult Male	100 Repetitions of Maximum Concentric Knee Joint Extension Voluntarily to Induce Muscle Fatigue.	Brazilian Propolis (BP) Supplement:787.5 mg (1^{st} Period)100 mg in (2^{nd} Period),1 Week Each Period.	A Decrease in Voluntary Maximal Torque Contraction Occurred Immediately After theTask and Recovery 2 Minutes After. Reducing Central Fatigue.
[18]	Elderly Women	Ageing Due to Old Age	BP 227 mg, Twice Daily for 12 Weeks	No Significant Impact On Grip Strength or Knee Extension. Increase SOD Activity.
[19]	Women with Type 2 Diabetes (T2D) and Dyslipidemia	Sports Training 3 Sessions/Week For 8 Weeks	Propolis 500 mg, 3 Times/Day for 8 Weeks	Increases Antioxidant Effects Through Increasing Malondialdehyde (MDA), Superoxide Dismutase (SOD), and TAC.Reducing Pro-Inflammatory Activity (IL-6) Through Upregulating CRTP-12 and SFRP5.
Animal Subjects and in Vitro				
[20]	Male DDY strain mice	Edema On Hind Foot with Carrageenin Injection	Propolis 1:1000 and 1:100 Orally	Inhibition of L-arginine, A Substrate of NOS Plays a Role in the Inflammatory Response.Anti-inflammatory Effects Via Inhibition of NO Production.
[21]	Male Wistar Strain Rats	Hind Legs Ischemia (Artery Clamp)	CAPE 10μmol/kg, 60 Minutes Intra-peritoneally Before Reperfusion Occurs	Decreased levels of MDA and NO. Increased SOD Activity.
[22]	L6-mouse myoblasts	-	CAPE 10μM	Increasing Glucose Uptake Via the AMPK Pathway and Activates the AKT Pathway in Myoblast Cells.
[23]	Male Wistar Strain Rats	Hind Legs Ischemia (Torniquet Application)	CAPE 10μmol/kg, 30 Minutes Before Reperfusion Occurs	Histological Damage Scores, Muscle Edema Percentage, Tissue MDA Content, Apoptosis Index, andNeutrophil Infiltration and Interspaces Decreased.
[24]	Female Wistar Strain Rats	Spinal Cord Injury	PEE China 0.2; 1 or 5 mg/kg, once a day for 3 weeks	Locomotion improvements seen on the Basso, Beattie, and Bresnahan (BBB) scale.
[25]	Female Wistar Strain Rats	Treadmill 16 m/minute Up to 90 Minutes/Day with Breaks	CAPE 5 mg/kg or 10 mg/kg for 5 Days	Reducing the Formation of MDA and MPO. Decreased Inflammation Via NFκB Pathway, By Reducing Cyclooxygenase-2 (COX2), Inducible Nitric Oxide Synthase (iNOS), Interleukin-1β (IL-1 β), and Monocyte Chemotactic Protein-1 (MCP-1) Expression.

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[26]	Male SD Rats	Treadmill for 60 Minutes, 5 Times/Week, for 6 Weeks	Propolis 50mg/kg WB/day, Parallel with Exercise	Increases Glycogen Use in Muscles. Increases the Antioxidant Activity of SOD, Glutathione Peroxidase (GPX), and Catalase (CAT) with MDA Declines
[27]	Female Wistar Rat	Sciatic nerve injury	Propolis 200 mg/kg BW	Improvement in Walking Function
[28]	C2C12 and RAW264 Cells	Induction of Ik-B (IKK) Inhibitor BMS-345541, to NF-Kb Activation	PEE Brazilian 100 µg/ml	Promote Myoblasts to Secrete Cytokines and Chemokines for Muscle Remodeling.Increases RAW264 Migration Which Stimulates the Production of Vascular Endothelial Growth Factor (VEGF-A) and MMP-12
[29]	Male C57BL/6 Mice	High-Fat Diet	Propolis 0.2% in Diet for 2 and 5 Weeks	Downregulates TLR4 (Toll-Like Receptor) Pathway Reduces Inflammatory Cytokines Expression
[30]	Male Wistar Rats	Hind Limbs Unloading	BP 500 Mg/Kg, 2 Times/Day at 6-Hour Intervals, for 2 Weeks	Stimulating Pro-Angiogenic Factors and Suppressing Anti-Angiogenic Factors to Prevent Capillary RegressionIncreasing Ratio Capillaries to Muscle Fibers, Volume, and Diameter Capillary Antioxidant Activity (Suppress P53 and SOD-1)
[31]	Male C57BL/6NCr Mice	Methylglyoxal (MGO) to increase AGEs	BP 0.1% in the Diet for 20 Weeks	Increase Muscle Mass. Decrease Accumulation of MGO, and Increase Glyoxalase Activity. Reduces Pro-inflammatory Responses.
[12]	C2C12 Cells	H_2O_2 Induction	PEEB 1, 3, and 10 µg/ml	Increased HO-1 Expression. Prevents ROS Production and Myoblast Cell Death Increases Cell Viability.
[32]	Male SD Rats	Sciatic Nerve Damage	Propolis-gum Arabic Nerve Guidance Channel	Increased SFI Score Related to Muscle Function.Increasing the Weight and Diameter of Muscle Fibers
[3]	Male Mice	Homozygous Diabetes	BP 0.08%, 0.4%, and 2% w/w in Feed, for 8 Weeks	Increased Grip Strength and Weight Muscles.Reduces the Expression of Genes That Play a Role in the Formation of Atrophy and Inflammation in Muscles.Increase Amino Acid and Inhibit Mitochondria Dysfunction.
[33]	Mouse C2C12 Cells	D Galactose (D-Gal) Induction	Propolis Ethanolic Extract Brazilian (PEEB) 0.1, 5, and 25 µg/ml for 48 Hours	Increase the Viability of C2C12 Senescent Cells.Reduces the Number of Senescence-Associated Beta-Galactosidase-Positive Cells. Stimulates C2C12 Cell Differentiation. Increase the Activation of Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2)/ Heme-Oxygenase -1 (HO-1) Signals to Maintain Cell Differentiation Ability Inhibit Cell Apoptosis.

Propolis also contributes to glucose and muscle metabolism. Propolis suppress blood sugar increase by stimulates GLUT4 translocation through PI3K and adenosine 5′-monophosphate-activated protein kinase (AMPK) signaling [1, 18]. Propolis prevent obesity-induced sarcopenia by enhancing mitochondrial efficiency within skeletal muscle tissue also via AMPK activation propolis-induced fat loss [3, 18]. When administrated for 20 weeks in feed in conjunction with magnesium oxide (MGO), propolis inhibits the formation of advanced glycation end products (AGEs) [32], thus alleviating muscle fatigue [17]. Propolis contain Artepillin C, a bioactive mono-phenol which has been found to decrease muscle fatigue in both skeletal and

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heart muscle by removing Reactive Organic Species (ROS) from the mitochondria, though the full mechanism remains unclear [17]. The anti-inflammatory benefit of propolis is also observed. Propolis administration suppresses the production of pro-inflammatory cytokines mRNAs, specifically affecting IL-1, IL-6 and the ratio of IL-6 to IL-10 [15, 19]. Propolis increases the concentration of C1q/TNF-related Protein-12 (CTRP-12) and excreted frizzled-related proteins (SFRP15) as anti-inflammation agents [19]. Consumption of propolis has been shown to decrease the level of circulating lipopolysaccharide (LPS), the activation of the Toll-like receptor 4 (TLR-4) pathway, and the expression of pro-inflammatory cytokines in the muscle tissues of mice fed a high-fat diet [29]. Research in Deutschland, Denken, and Yoken (DDY) mice has demonstrated that propolis can decrease inflammation by blocking the production of nitric oxide (NO) following intra-plantar injection of carragenin [20]. Additionally, research has found that CAPE can inhibit the expression of i-NOS, by suppressing NFκB activation. Moreover, the parameter for neutrophil sequestration in ischemic tissue undergoing reperfusion, myeloperoxidase (MPO), increased during the ischemia, leading to the production of oxidants by neutrophils. Propolis has been found to decrease neutrophil infiltration and suppress MPO activity in muscle [20](Figure 2).

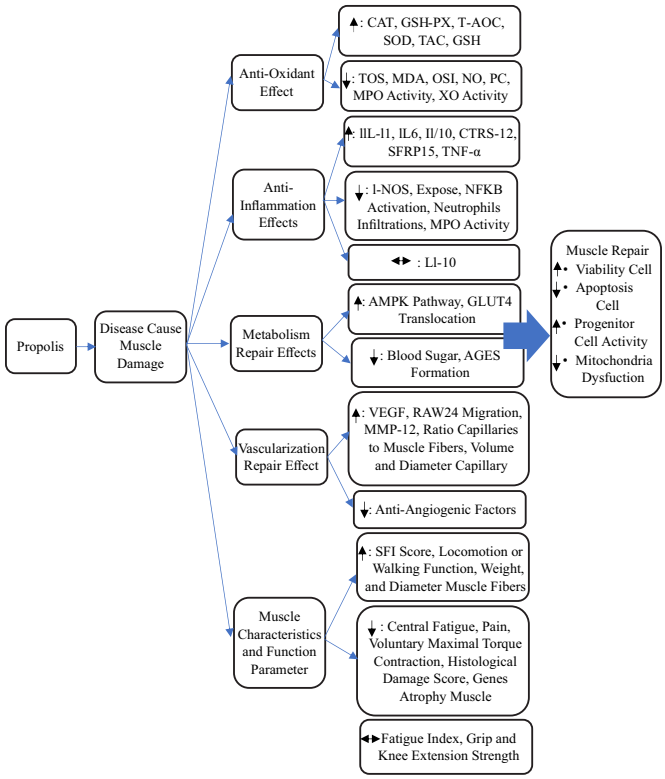

Figure 2: Effect of Propolis On Muscle Damage (↑: Increase, ↑: Decrease, ↔: Non-Significant)

DISCUSSION

From the 21 articles in this study, it is possible to ascertain the role of propolis in muscle repair through three main mechanisms, primarily due to its antioxidant, and anti-inflammatory properties, and its effect on the metabolic system including glucose and lipid metabolism, which influence muscle fatigue, strength, and mass. As an antioxidant, propolis showed benefits in various cases including muscle stress, exercise and the ageing process. Research indicates that administering propolis during skeletal muscle-induced stress elevates the levels of antioxidants including catalase (CAT), glutathione peroxidase (GSH-PX), Total Antioxidant Capacity (T-AOC), heme oxygenase-1 (HO-1) and superoxide dismutase (SOD) [33, 34]. This increase in antioxidants enables cell survival by blocking the p53 and protects the muscle cells from apoptosis thus facilitating the repair process [29]. Furthermore, propolis intervention in exercise-induced skeletal muscle has been shown to elevate TAC and GSH levels, while reducing Total oxidant status (TOS), malondialdehyde (MDA) and Oxidative stability index (OSI) levels following the 12-minute runs (Cooper test) [16]. Administration of propolis also showed benefits in ageing people. A 12-week propolis intervention in elderly women resulted in increased SOD levels suggesting its potential benefit for the ageing process [18]. Vascularization is one of the crucial factors that facilitate tissue repair, including in muscle. Propolis can be used as a cytoprotectant for endothelium of vascular within skeletal muscle. Muscle capillary is influenced by pro-angiogenic signals like VEGF, which promotes the differentiation of endothelial cells, a crucial step in muscle repair [30]. Therefore, this mechanism of action is also described as the benefit of propolis in muscle repair. The study revealed the benefits of propolis in muscle strength and mass. Results from examining muscle strength specifically grip strength and knee extension strength in elderly women who received propolis supplementation, showed no significant differences. The lack of quantitative data on physical activity during the trial period, is responsible for these results, suggesting additional research may be necessary [18]. Research on peripheral nerve damage and spinal cord damage in animal models found that treatment with propolis resulted in improved muscle function as measured by the SFI score [32], morphologically and histologically increased muscle mass, and enhanced locomotion [24]. Following 20 weeks of treatment with propolis, there was an observed increase in soleus muscle mass, however, it was not attributed to muscle hypertrophy, instead, it is thought to be a result of stimulation of glycogen accumulation within the muscles [31]. The rise in muscle mass might also be attributed to an increase in connective

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tissue resulting from the migration and proliferation of fibroblast due to propolis administration. Further exploration is required to investigate another potential mechanism. The majority of studies mention that active ingredients of propolis such as Artepellin-C, CAPE, coumaric acid, trans-phenolic acid, and kaempferide are components of propolis that play an important role [15, 34]. Some studies use these components singly to prove their effects. The active components contained in propolis have different properties and concentrations because propolis itself is very dependent on the demographic location of the distribution of flora [35]. Therefore, according to the author, other components contained in propolis also have an important role that is considered as a wholeness of the material [36]. There are many variations in the time used to see the effects of propolis on muscle repair. Studies conducted on human populations themselves vary from 4 weeks to 12 weeks. However, from studies that looked at the effects of propolis on anti-inflammation conducted for 30 days, there was a decrease in pain caused by inflammatory activity [15, 18]. From the studies traced, the effect of propolis on insignificant parameters is due to the lack of facilities and infrastructure, as well as the lack of supporting data. The direct effect of propolis on these conditions is not explained in detail [15]. However, according to the author, data on muscle function that is not yet significant can be influenced by various factors, including individual habits. Therefore, further testing is expected on a wider population with good sample characteristic control.

The included studies show heterogeneity in design, dosage, duration, and outcome measures, limiting comparability. A majority of evidence is derived from animal and cell-based studies, reducing clinical applicability. Lack of standardized propolis formulations and insufficient control of confounding factors (e.g., physical activity) further affect conclusions. Future research should focus on large-scale randomized controlled trials in humans, standardized dosing protocols, and exploration of long-term effects on muscle function and recovery.

CONCLUSIONS

It was concluded that the bee's natural product, propolis, has several advantages in muscle repair due to its multiple mechanisms of action, encompassing antioxidants, anti-inflammatory properties, impact on muscle glucose metabolism, and stimulation of angiogenesis.

Authors' Contribution

Conceptualization: PRA, SK
Methodology: SK, PRA, DS
Formal analysis: DS
Writing and Drafting: PRA, DS, SK
Review and Editing: PRA, DS, SK

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

All the authors declare no conflict of interest.

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