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# Bone broth extracts importance for consumers health

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## *ABSTRACT*

The basis for studying bone broth extract lies in its growing acceptance as a functional food that can contribute to human health, controlling or preventing illness non-communicable. The research reviews the scientific literature to find work promoting bone extract use for health improvement. Compilation aims to understand its nutritional composition, processing, applications in the food industry, and the associated risks; such as contamination by heavy metals and antibiotic residues in the bones used. Likewise, broth's potential as a source of nutrients is being investigated beside the general consumers, and for the development of food products that may be aimed at consumers with special dietary regimes.

**Contribution/Originality:** Generally, the information of bone extract leads to its composition to specific a bone type. This review is a compilation of different bone types, showing several technological aspects and restrictions for their transformation and use as a functional food for controlling and prevents illness.

## 1. INTRODUCTION

Bone broth is liquid elaborated from cooking the animal bones and connective tissue. Anthropologists think people drank liquid infused with bones and other animal parts as early as prehistoric times and it has been used since the beginning of humankind [1]. Therefore, bone broth history goes back thousands of years, its consumption has been around for centuries by native people in North America [2] and in the Traditional Oriental Medicine [3].

From the oriental medicine perspective, some of the main benefits of bone broth, include boosting a person's qi, blood, yin, and even essence. Qi, yin, and yang, which are the roots of Traditional Chinese medicine, are aspects of a person typically depleted with chronic conditions such as chronic fatigue syndrome (CFS) and through the normal aging process. In the view of Oriental medicine, chronic fatigue syndrome (CFS) is thought to result from a state of unbalanced inter-organ functions, or a condition of deficiency in the qi or blood characteristics [3]. Qi is translated as "vital energy" and the yin and yang are the harmony of all the opposite elements and forces that make up existence [4-6].

From the occidental point of view, broths are believed to be a valuable source of micronutrients [7]. In modern nutrition bone broth extracts have gained relevance, standing out for their rich composition and health benefits.

The vitamins, minerals, and collagen from bone broth have quite healthy benefits for the human body. Even bone fat has benefits and several names are used to describe those obtained from boiled bones, such as; bone broth extract, bone grease, bone marrow, bone butter, bone soup [2].

Although the health benefits of bone broth have been known for a long time, only about twenty years ago, its healing effect began to be scientifically studied, for example, it has been discovered that the generally accepted healing effect of chicken soup against symptomatic upper respiratory tract infection is due to increased velocity of the nasal mucosa or its mild anti-inflammatory effect [8].

This nutritious liquid is obtained by prolonged cooking in an aqueous medium of animal bones; such as beef, pork, chicken, and fish, among others. It prolongated cooking which allows the extraction of a variety of essential nutrients. As it is cooked for longer, it obtains a denser consistency attributed to its higher collagen content. The nutritional composition of bone broth varies significantly depending on factors; such as cooking time, temperature, and the type and combination of bone used [9-11].

More recently, bone broth extracts have increasingly been recommended as part of diets for patients with gut and psychology syndrome (GAPS), such as those with autism and attention deficit hyperactivity disorder (ADHD) [12]. The meat stock, rather than bone broth, is used in the beginning stages of the GAPS Diet™, especially during the introduction diet, where the primary focus is healing the gut, and the bone broth is ideal for consuming once gut healing has taken place [13].

However, it is important to mention on the use of bones for human consumption, there exist regulations, which poses challenges and opportunities for future research. Therefore, investigating and compilating information on its manufacture and chemical composition would form a useful study, that could be a convenient component in the prevention and control of non-communicable diseases. Moreover, innovations such as presentation in flour and, formulations ready-to-cook will also be useful for older or sport consumers, among others.

## 2. DEFINITION: BONE BROTH, EXTRACT, STOCK AND SOUP

Several terms are associated with the mix of bones with water. As a function of its thermal process and composition, they are found in literature; such as stock, broth, broth extract, and soup. Therefore, it is important to define the terminology related to the products obtained from the cooked mix of bone or meat with water.

Bone broth, meat broth, and stock are built on the same recipe: water, meat, or bones (or both), with or without vegetables and seasonings. As it is cooked, the liquid is typically skimmed (although this is not necessary since the scum that rises to the top of the stock pot– off-putting as it is – is a rich source of amino acids) and eventually the solids are removed by straining the stock with a fine-mesh sieve or reusable coffee filter [13].

Broth is typically (traditional soup broth) made with meat, and can contain a small number of bones and cooking with vegetables and seasonings.

Bone Broth Extract is a nutritious liquid obtained from the prolonged cooking of bones from animals such as beef, pork or chicken, fish and others in water [14]. The bone broth is simmered over low heat for 8 to 24 hours, at a temperature ranging from 85 to 100°C [15, 16]. This prolonged cooking allows a greater amount of nutrients to be extracted from the bones, including minerals such as calcium, phosphorus and magnesium, as well as essential amino acids, to which beneficial health properties are attributed [17]. Broth obtained from chicken and cattle bones are the most consumed worldwide [18].

Stock is made by simmering meaty bones with other ingredients in water until it forms a flavor-rich liquid. It typically cooks for less time than bone broth, and it is used as a foundation for other foods.

Soup is a primarily liquid food, generally served warm or hot (but may be cool or cold), elaborated by combining and cooking ingredients of meat or vegetables with stock, milk, or water.

## 3. BONES STRUCTURES

Bone is a mineralized connective tissue that exhibits four types of cells: osteoblasts, bone lining cells, osteocytes, and osteoclasts [19]. It is a dynamic tissue that performs mechanical, biological and chemical functions [20].

Depending on the species, age, and type of bone, bone cells represent up to 15% of the bone volume; in the mature bone of most animals, they usually represent only up to 5%. The non-living intercellular material of bone is formed by collagen, with small amounts of protein polysaccharides, glycoaminoglycans chemically linked to proteins and dispersed within and around the collagen fibers, and an inorganic mineral component in the form of crystals [21]. All bones have an outer layer called the cortex, which is smooth, compact, continuous and of variable thickness.

The macroscopic structure of mammalian bone is composed of two types of bone: cortical and spongy. The cortical bone is hard and serves as a place of attachment for the muscles; Theoretically, it is divided into three zones: the periosteal zone or external portion, the mesosteal zone or central portion, and the endosteal zone or internal portion [22]. Cancellous bone, also called spongy or trabecular, is composed of an arrangement of bone spicules called trabeculae. Cancellous bone is located inside the bone, including the ends of long bones, the inside of cuboidal and flat bones, and between the inner and outer layers of cortical bone in the skull [22].

The structure of bones and cartilage that supports the fish body is known as the fish skeletal system. Some fish which are formed of only bones are called bony fishes, while those formed of cartilage are called cartilaginous fishes [23]. In contrast to the bones of all tetrapod and evolutionarily primitive fish, many of the evolutionarily more advanced fish have bones that do not contain osteocytes. Imaging techniques have shown that anosteocytic fish bone (a type of bone that doesn't contain osteocytes, and is also known as "acellular" bone) is composed of a sequence of planar layers containing mainly aligned collagen fibrils, in which the prevailing principal orientation is progressively [24].

## 4. CHEMICAL COMPOSITION OF BONES

Bone is a complex cellular tissue that contains, by weight, approximately 30% organic constituents and 70% minerals. The most abundant protein in the organic compartment is type I collagen, a fibrillar structure. Collagen represents 98% of the organic phase of bone, and various non-collagen proteins account for the remainder [25].

Representing between 10 and 20% of the animal's body weight, the livestock and poultry bones are byproducts produced during meat processing and slaughter and are a rich source of highly nutritious natural elements [26].

The fresh bones from livestock and poultry are rich in nutrients such as proteins, fats and minerals (lot of calcium, sodium, iron and phosphate salt, magnesium), bioactive substances, and vitamins with a water content between 45 and 60%, collagen between 20 and 30% and minerals (the main ones are calcium and phosphorus) representing the 20% of the nutrients in cattle and poultry bones [27].

Chimegee and Dashmaa [17] in their study found that beef broth (not concentrated) provides approximately 4.17g of protein per 100mL, and provides 83.15mg of essential amino acids per 100mL.

The mineral phase of bone is approximately 95% hydroxyapatite, a highly organized crystal of calcium and phosphorus. The calcium and phosphorus content in bones is 19.3% and 9.39% respectively. Other minerals normally found in bone include sodium (approximately 30% of total body sodium can be stored in bone crystal), magnesium, and fluoride [25].

### *4.1. Proteins, Fat and Minerals Contents*

90% of the protein in animal bones is collagen, ossein, and chondroitin, minerals, bioactive substances, and vitamins. On the other hand, bone marrow is a soft, sponge-like tissue in the center of most bones that produces blood cells composed of phospholipids, and a phosphoprotein essential for the human brain [26, 28, 29].

Kakimov, et al. [26] studies shown the chemical and mineral composition of chicken (necks, thighs, wings, breasts) and beef bones. The authors reported that crude protein, and crude fat content were higher in poultry than in beef in contrast with the mineral such as calcium, magnesium, and iron which were higher in the beef. Bone fat is

mainly concentrated in the bone marrow. The peculiar characteristic of bone fat is the high lecithin content compared to other fatty materials.

In adult mammals, approximately 20% of the wet weight of bone is water, 45% is ash, and 35% is organic matter. Calcium contributes 37% of the ash content and phosphorus 18.5%. On a dry weight basis, the mineral content is 65 to 70% and the organic matter is 30 to 35% [30].

Jensen, et al. [9] and Toppe, et al. [31] have pointed out differences among the aminoacidic profile of bone from different fish type; blue whiting, small herring and mackerel have lower levels of the collagen-associated amino acids glycine, proline and hydroxyproline, and higher levels of tyrosine, valine, isoleucine and tryptophan. Horse mackerel is different from the other species that were analyzed, since it has higher levels of glycine, alanine, proline, hydroxyproline and cysteine, and lower levels of histidine, tyrosine and isoleucine. Comparing small and large fish (saithe and herring), large fish (of the same species) contain lower levels of protein and a higher level of ash.

Chimegee and Dashmaa [17] in their study found that beef broth (not concentrated) provides approximately 4.17g of protein per 100mL, and provides 83.15mg of essential amino acids per 100mL. The crude protein of beef bone broth mainly includes chondroitin, collagen, and free amino acids [32].

Mar [18] in his studies determined the content of proteins, amino acids (content and profile) and minerals present in the bone broth obtained from cooking bovine femur for 8 continuous hours at 100 °C. The results show that of the solids present 7.51% belongs to minerals, while 74.62% corresponds to protein, the author also determined that the 69.92% of the solids present were amino acids (Table 1).

**Table 1.** Nutritional content of bone broth obtained from bovine femur.

| Nutritional content | mg/100mL | % |
|---|---|---|
| Protein | 248.5181 | 74.62 |
| Amino acids | 232.8671 | 69.92 |
| Minerals | 25.0176 | 7.51 |

**Source:** Mar [18].

From the same studies of Mar [18] Table 2 shows the aminoacidic profile of the bovine femur broth. The result showed 17 of the 20 amino acids make up proteins were analyzed. This table shows that each 100 mL of bone broth provides a total of 232.8671 mg of AA; where 55.56% corresponds to essential amino acids and 44.43% to non-essential amino acids. The main amino acids found in bone broth were glutamic acid (Glu), Histidine (His), Arginine (Arg), aspartic acid (Asp), lysine (Lys), glycine (Gly), threonine (Thr) and valine (Val ), which are found at a concentration greater than 14 mg/100 mL, while those with the lowest concentration were alanine (Ala) and isoleucine (Ile).

**Table 2.** Bone broth amino acids from bovine femur.

| Amino acids | mg/100mL | Amino acids | mg/100mL |
|---|---|---|---|
| Asp | 16.7499 | Thr | 14.7519 |
| Glu | 50.1499 | Arg | 17.2827 |
| Ser | 6.8265 | Val | 14.1858 |
| Gly | 15.0183 | Met | 9.2907 |
| Ala | 2.5974 | Ile | 3.0969 |
| Pro | 3.3966 | Leu | 4.6620 |
| Cys | 3.4632 | Phe | 7.0596 |
| Tyr | 5.2614 | Total AA | 232.8671 |
| Lys | 15.0849 | Essential amino acids | 129.4039 (55.56%) |
| His | 43.9893 | Non-essential amino acids | 103.4632 (44.43%) |

**Source:** Mar [18].

The bone fraction of fish has a high mineral content that may be suitable as a natural source of calcium [9] as well as the bone matrix protein collagen [31]. Fish bones generated in the fishing industry after filleting represent approximately 30% of the total weight of the fish.

Toppe, et al. [31] found that the levels of calcium, phosphorus and magnesium were lower in the bones of salmonid species (salmon and trout), showing ranges of 135-147 g/kg for Ca, 81-87 g/kg for P and 2.2-2.4 g/kg for Mg in lipid-free dry matter. The corresponding levels in lean fish species were: Ca: 186 ± 15 g/kg, P: 102 ± 14 g/kg, Mg: 3.1 ± 0.1 g/kg. However, potassium (K) levels were highest in salmon and trout, ranging from 7.7-8.2 g/kg. Horse mackerel showed the highest levels of Ca (233 g/kg) and Mg (3.6 g/kg). Blue whiting had the lowest level of K (2.6 g/kg). Cod and saithe species showed Ca, P, Mg and K ranges of 190-199, 108-113, 3.0 and 4.9-5.2 g/kg, respectively. The level of Ca in the ash is similar in all species, ranging between 304 g/kg of ash in salmon and 325 g/kg of ash in saithe, except in large herring and horse mackerel, which have Ca values of 367 g/kg of ash. In general, the bone mineral matrix contains similar levels of the main structural minerals, Ca and P, giving a similar Ca/P ratio in all fish bone samples analyzed.

### *4.2. Collagens, Glucosamine and Chondroitin Sulfate*

Collagen is the most abundant structural protein in living beings, making up approximately 30% of total proteins. At least 29 types of collagens have been identified, varying considerably in their amino acid composition, amino acid sequence, spatial structures, and function [33]. Among all those different types of collagens, type I is the most common in mammals, widely distributed in bones, skin and tendons [33]. A distinctive feature of collagen is the high content of proline and oxyproline [34].

As postulated by Aubry, et al. [35] collagen peptides from animal tissues such as skin, tendons, cartilage, bone, etc., have been screened worldwide for numerous biological activities and the authors have pointed out that assessing the effect of age and anatomy of collagen-rich tissues can promote a better application of collagen bioactive peptides. Therefore, they have investigated the effect of bovine bone age, its anatomy, and collagen hydrolysis with different enzymes, on the antioxidant activity of collagen peptides. The authors concluded that age and anatomy of the animals showed a significant effect on antioxidant activity; anatomy becomes most important with age. They also reported that a greatest number of peptides was released from young bones' collagen hydrolysed with papain and that the antioxidant activity was higher at higher temperatures, except for meat proteins.

Rozi, et al. [36] produced bone marrow powder from four kinds of animal leg bone (bovine, horses, sheep, and camels). The proteins and peptides were isolated and characterized from the bone marrow powder by sodium dodecyl sulfate-polyacrylamide gel electrophoresis.

From the result the authors postulate that horse bone marrow protein showed the highest free amino acid content (49.7 mg/g), and antioxidant activity to DPPH (2,2-difenil-1-picrilhidracilo) free radical. Rozi, et al. [36] also pointed out that the amino acid composition ratio approached the Food and Agriculture Organization/World Health Organization (FAO/WHO) ideal amino acid pattern recommendation. Moreover, the authors claims that most of the obtained fractions showed antimicrobial activities (towards Escherichia coli and Candida albicans).

Bone glycosaminoglycans consist mainly of chondroitin sulfate and small amounts of hyaluronan [37]. If connective tissue, such as tendons, ligaments and cartilage, is still attached, the bones in the broth will provide our bodies with raw materials for the formation of skin, bones and cartilage, including keratan sulfates, dermatan sulfates, sulfates of chondroitin and hyaluronic acid [38].

Glucosamine ($C_6H_{13}NO_5$) or 2-Amino-2-deoxy-D-glucose chitosamine, is a natural amino sugar that is present in the body preserving the integrity of the cartilage. Glucosamine sulfate is part of the group of glycosaminoglycans (GAGs), which are important structural constituents of the extracellular matrix of cartilage [39].

Chondroitin is a biomolecule that is found naturally in the human body and is an important structural constituent of the extracellular matrix of cartilage and provides cartilage with its mechanical and elastic properties [40].

## 5. BONE BROTH TOXIC SAFETY

### *5.1. Heavy Metals*

The content and level of accumulation of heavy metals in the animal's body depend on the type of food consumed and the type of feeding, as well as the area where it is raised and the climatic conditions. Toxic elements such as lead (Pb), chromium (Cr), mercury (Hg), nickel (Ni), cadmium (Cd) and arsenic (As), are often associated with pollution and can have effects dangerous in living organisms when specific concentrations are exceeded [41, 42].

It is important to determine the toxic safety of bone broth, for example, there are calcium supplements made from bone meal that have lead levels ranging from about 10µg/g, and some even contain cadmium (approximately 2µg/g). Therefore, it is reasonable to assume that simmered animal bone broths contain toxic metals causing dietary exposure [12].

Heavy and toxic metals that enter the animal's body accumulate mainly in the bones, liver, and kidneys [26]. The concentration of heavy metals studied in the tissues of animals of different species (cows, pigs, birds) was detected in the kidney, and at the time of that study none of the tissues that were positive for heavy metals exceeded the levels of tolerance limits [43].

Hsu, et al. [12] evaluated the essential and toxic metals in animal bone broths, to determine the associated risk with its consumption. The authors carried out three series of controlled experiments to study the factors (cooking time, acidity, type of bone and animal species) that influence the extraction of metals. The result shown that the doses of toxic metals ingested are minimal in these broths are in the range from a few µg (Pb and Cd) to hundreds of µg aluminum (Al) per serving. These levels are lower than the respective reference doses [Minimal Risk Level (MRL)], resulting in low-risk ratios.

In other study realized by Kakimov, et al. [26] no levels of heavy metals in meat and bone paste were found that exceed the established limits or that are considered dangerous for health (Table 3). The lead content was 0.071 mg/kg and 0.056 mg/kg, the arsenic content was 0.016 mg/kg and 0.011 mg/kg. These values correspond to the maximum accepted limits regarding the content of toxic elements.

**Table 3.** Content of toxic elements in meat and bone paste.

| Toxic element (mg/Kg) | Criterion according to regulations (mg/Kg) * | Meat and poultry bone pasta (mg/Kg) | Beef meat and bones pasta (mg/Kg) |
|---|---|---|---|
| Lead | 0.1 | 0.071 | 0.056 |
| Arsenic | 0.1 | 0.016 | 0.011 |
| Cadmium | No reported for bone or meat | Non detected | Non detected |
| Mercury as metil mercury | 0.05 (Reported for fish) | Non detected | Non detected |

**Note:** *Codex 193-1995.
**Source:** Kakimov, et al. [26].

Therefore, the health risks associated with ingesting toxic metals from a portion of these broths are considered minimal, with no interactive effect assumed between them.

The presence of toxic metals in bone broth has been less studied, so it is important to do so to address some of the concerns about whether bone broth, apart from being a good source of nutrients, has any associated risks with its consumption.

### *5.2. Antibiotics in Bone Broth*

Another concern concerning the use of bone broths is the presence of antibiotics. Last decades veterinary science has been applied the use of antibiotic in the prevention of infections and supposed growth promoters have caused an increase in bacterial resistance. Antibiotic residues in food products of animal origin are of public health importance due to the adverse effects they have on humans [44, 45]. The wide use of antibiotics that are present in the edible tissues of animals, leads to problems for consumers with allergic responses or hypersensitivity to them.

There is a group of antibiotics that are lodged in the animal bones, so it is essential to obtain information on the levels of antibiotic residues in bone broth [43].

Although studies on antibiotic residues focus on edible animal tissues (such as meat, liver, kidney, and muscle), it is important to consider their presence in bone broth [46, 47].

The most commonly used antibiotics, such as tetracyclines, have a high affinity for bone tissues, where they can accumulate [48]. Research has shown that heat treatment [49] can reduce antibiotic residues. However, it is essential to perform specific analyzes on bone broth to ensure the quality of the final product.

## 6. BONE PROCESSING TECHNOLOGY

Currently, Regulation (EC) No. 1069/2009 [50] prohibits the use of animal bones, including chicken bones, for human consumption [50] but Food and Drug Administration (FDA) guidelines state that chicken bones can be used in certain food preparations, such as soups, stews, and broths.

However, the increment of research has shown evidence of the health benefits of the components of the bones of different animals, plus the high percent of waste from the meat and fish processing and the industry makes the use of these bones attractive as functional foods (an animal produces about 10–18% of its total weight in bone waste).

The complete processing within the slaughtering of livestock and poultry and the waste raw materials such as bones allows for expanding the range products with a low prime cost, thereby promoting to the sustainable development of agroecology by applying the waste hierarchy the three R: Reducing, Reusing, and Recycling [51].

Moreover, more scientific research and processes may allow the safe use of bones for human consumption [7]. Therefore, the development and utilization of livestock and poultry bones have received global attention, and developed countries are working on the development of by-products from bones [29, 52, 53]. On the other hand, the processing of aquatic products is associated with the waste of a large number of fish heads and bones, which account for about 45% of the waste [54].

Bone processing technology has been applied to process many foods derived from bones, such as bone paste [55, 56] bone protein, and bone powder [57]. Also, in Japan, bones from animals such as pigs, cows, and chickens are processed into a wide variety of foods, such as bone paste, bone meal, bone flavoring, bone-flavored juice, and bone-flavored protein meat. These bone-infused foods have evolved into desirable nutritional and health products, gaining wide acceptance in society [27].

Cheng, et al. [58] studied the extraction temperature, and time effect on the pH value, soluble protein content, peptide content and antioxidative properties of chicken leg bone extract. The authors report no significant differences ($p<0.05$) in the pH by effect of treatments. However, the protein content decreased during cooking at high temperatures (90-100°C), and long times (10-15 minutes); in contrast with the antioxidative properties, which exhibited superoxide anion scavenging ability, DPPH free radical scavenging ability, reducing capacity and inhibitory activity of linoleic acid peroxidation significantly higher ($p<0.05$).

Bone protein is a significant secondary product of the meat industry. Begum, et al. [59] have pointed out that enzymatic hydrolysis is a useful technique to elaborate peptides that have a high level of purity and are chemically stable, and if they are broken down through enzymatic hydrolysis, they can generate antioxidant peptides with acceptable viscosity. Therefore, it is believed that the smaller molecular weight collagen, i.e., collagen peptide (CP), has more potent activity than native collagen [60].

Moreover, Nie, et al. [61] had before demonstrated the improvement of the antioxidant activity of chicken bone protein hydrolysate and its peptide fractions via the Maillard reaction using galactose claiming that its improvement could be closely related to its molecular size.

In the Deng, et al. [62] review it is summarized the recent advances in antioxidant collagen hydrolysates development; such as, preparation process of antioxidant collagen hydrolysates. They also reviewed the effects and the mechanisms of amino acid composition and collagen peptide structure on the antioxidant activity of collagen hydrolysates, and the applications of antioxidant collagen hydrolysates in biomedical domains.

The studies of Carrera-Alvarado, et al. [63] pointed out that the application of pepsin pretreatment before enzymatic hydrolysis is an effective method for the production of bioactive compounds from bone sources. The results obtained by the authors show that peptide extracts of ham bone hydrolysates have antioxidant and dipeptidyl peptidase-IV (DPP-IV) inhibitory activity, which could be used as bioactive ingredients in functional foods.

Chen, et al. [64] pointed out that the soluble protein, peptide, amino acid and total phenol content, as well as the antioxidant capacity (DPPH, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS)+ radical scavenging activity, and relative reducing power), were significantly increased on the fishbone after its fermentation with *Monascus purpureus* (species of mold that is purplish-red in color).

Far ahead, Jensen, et al. [9] produced protein hydrolysates from the spines of hake, cod, and salmon with potential bioactive properties. The author aimed to study the content and bioavailability of minerals and proteins in the hydrolysates. Results indicated that bone protein hydrolysates contain bioavailable proteins and minerals, emphasizing that bone powder products generated from enzymatic hydrolysis have a high content of calcium (15.7-21.6g/100g), followed by phosphorus, potassium and magnesium.

Previous studies by Šližytė, et al. [65] on cod (Gadus morhua) backbones had evaluated the effect of storage (fresh or frozen) and preparation (hydrolyzed at different times; 10, 25, 45 and 60 min) on the yield, functionality, bioactivity and antioxidative properties of the fish protein hydrolysates. The authors had pointed fresh raw material significantly increased the yield of dry fish protein hydrolysates with better color and emulsification properties. They also showed long time of hydrolysis gave higher fish protein hydrolysates yield, increased degree of hydrolysis and decreased water holding capacity of the powders. Among the hydrolysis times tested, 25- and 45-min hydrolysis demonstrated the best emulsification properties.

Xu, et al. [66] review shown that by-products of aquatic animals have high research value in the field of natural bioactive molecules and they discuss new extraction processes such as ultrasonic, microwave, supercritical extraction, high voltage pulsed electric field technology, among others can be applied to improve the extraction rate and industrialization of collagen peptides in combination with each other. In addition, combinations of two or more enzymes during enzymatic digestion have been shown to produce low molecular weight peptides that readily penetrate the intestinal tract, resulting in beneficial health properties.

Amitha, et al. [54] have studied the nutritional composition of power from grouper thorns, swordfish and white snapper bones extracted by two different methods (water and alkaline solution). Results shown that the percentage of crude protein in the fish bone powder extracted with alkaline solution was very low as compared to extraction with water: 8.75% (swordfish), 6.57% (white snapper), 3.28% (grouper thorns) for an alkaline extraction method, and 25.16% (grouper), 19.69% (swordfish), 16.49% (white snapper), water extraction. The authors conclude that the extracted fish bone powder is nutritious and can significantly contribute to human health needs.

In general, the ultrasound-assisted enzymatic hydrolysis was an effective strategy to extract the bioactive peptides from porcine bone, and the inflammatory regulation capacity of bone collagen-sourced peptides was firstly demonstrated [67].

By using calcination techniques of wasted chicken bone blended with polysulfones (PSF) polymers, Zaman, et al. [68] obtained dahllite/hydroxyapatite/collagen filler as a highly biocompatible, and antifoulant hemodialysis membranes.

## 7. HEALTH BENEFITS OF BONE BROTH

The nutritional composition of bone broth varies according to the different ways of its preparation, such as the origin of the bones, the type of bone used, the cooking time, and temperature, the addition of ingredients that facilitate the extraction of nutrients. and finally, the processes involved with the final destination of the product, for example, freezing, drying, freeze-drying.

As was postulated by Ke, et al. [69] bone soup and/or broth is worldwide appreciated for its multi-purpose nourishing functions, besides the joyful taste, particularly in facilitating the prevention and treatment of inflammatory bowel disease, immune malfunction, Siebecker [70] and Morell and Daniel [71] glucose intolerance, and insulin in sensitivity in vivo [72].

Pork bone soup, as a traditional nutritious food in the East and West, has been widely used as a folk remedy for its proven functions in the prevention and treatment of inflammatory diseases and immune dysfunctions [70].

Jin et al., 2017 (cited by Ke, et al. [69]) pointed out that porcine bone soup exhibits intracellular antioxidant activities in epithelial cells, e.g., colon epithelial cellCaco-2 and Madin–Darby Canine Kidney (MDCK) cells, challenged by AAPH-induce peroxyl radicals.

McCarty and DiNicolantonio [16] pointed out that due to the amount of amino acids present, the bone broth has positive effect at the level of metabolic and cardiovascular health. On the other hand, the bioactive peptides hydrolyzed from bone collagen have been found to possess health-promoting effects by regulating chronic diseases such as arthritis and hypertension [73].

Ke, et al. [69] demonstrated that a large number of colloidal particles derived from bone soups were engulfed by murine oral macrophages in vitro and subsequently protected cells from oxidative stress. The results provide evidence of the direct interaction between food colloidal particles with immune cells, implying a possible new mode of food-body interaction.

Mizokami, et al. [72] study shows for the first time that boiled pork bones are a source material for osteocalcin in the large-scale production of supplements designed to improve glucose metabolism. Osteocalcin (OC) is a bone-derived hormone that regulates energy metabolism.

Collagen has a significant amount of glycine and represents a potential ingredient for Diabetes control. It has been postulated the glycine as a regulator of blood sugar, controlling gluconeogenesis and glucose production in the liver [74, 75] and as stimulator of the secretion of a gut hormone that potentiates insulin's effect on glucose removal from the circulation [76].

Gaspardi, et al. [77] aimed to evaluate differences in vitro biological potential as antioxidant, and hypoglycemic of commercial bovine, fish, and porcine collagen hydrolysates. The authors propose a new application for collagen hydrolysate with biological activities. However, authors claim for future studies on the additional benefits arising from collagen peptide consumption for the prevention of aging complications or hyperglycemic conditions as observed in chronic diseases, such as Diabetes Mellitus Type 2.

Later, Algehainy, et al. [78] have studied the nutritional composition; as well as, the potential therapeutic effect on Diabetes Mellitus Type 2 regression on albino rats of femur bone extracts from different animals (bovine, chicken, sheep and goat). In vivo data indicated considerably improved of the Diabetes Mellitus Type on rats, as seen by lower serum levels of liver disease index (TL, TG, TC, ALT, AST, ALP), bilirubin, creatinine, urea, Interleukin 6 (IL-6), tumor necrosis factor (TNF-α), Soluble intercellular adhesion molecule-1 (sICAM-1), and Malondialdehyde (MDA). The authors concluded that this research could result in the creation of a simple, non-

invasive, low-cost, reliable and early therapeutic applications method for control of Diabetes Mellitus Type 2 control.

Chicken soup has long been regarded as a remedy for symptomatic upper respiratory tract infections. Rennard, et al. [8] proposed that the broth made from chicken bones may also reduce the migration of immune cells during illness. The study, therefore, suggests that chicken soup may contain a number of substances with beneficial medicinal activity. A mild anti-inflammatory effect could be one mechanism by which the chicken soup could result in the mitigation of symptomatic upper respiratory tract infections [8].

Yoshimura, et al. [79] claims that chicken comb extract, which is rich in hyaluronan, not only relieves joint pain and other symptoms, but also potentially improves the balance of type II collagen degradation/synthesis in patients with knee osteoarthritis.

Studies by Lee, et al. [80] on monosodium iodoacetate-induced osteoarthritic rats, shown that deer bone extract has the potential to relieve the discomfort or the articular cartilaginous damage associated with osteoarthritic (OA) and may be useful as a natural supplement for OA treatment without serious side effects. The authors reported the significant diminution of the levels of serum pro-inflammatory cytokines (interleukin-1β, interleukin-6), and tumor necrosis factor-α by, inhibition of the expression of collagen type II and metalloproteinases, messenger ribonucleic acids (mRNAs) in the cartilage, once that the of deer bone extract was administered to the osteoarthritic rats.

Suh, et al. [81] have suggest that deer bone extract, which contains various components related to osteoarthritis, including chondroitin sulphate, may possess anti-osteoarthritic properties and be of value in inhibiting the pathogenesis of osteoarthritis. In a randomized, double-blind, placebo-controlled study of Shin, et al. [82] whom have evaluated the efficacy of deer bone extract in participants with knee osteoarthritis found that may mildly reduce joint pain and stiffness and improve joint function in patients with painful knee osteoarthritis.

Songür, et al. [83] measured the effect of a derivate from equine bone protein extract; an osteoinductive agent (Colloss-E) composed of a high amount of type-I collagen and other bone proteins, with that of human demineralized bone matrix for treating cavitary bone defects not requiring scaffold use. The authors used rabbit distal femoral condyle as a stable cavitary bone defect model and discovered that it was successful in treating cavitary bone defects not requiring scaffold use.

Heo, et al. [84] had shown that bonefish extract containing a trioligopeptide induces osteogenic activities. Therefore, these authors in 2019 elaborated a three-dimensional (3D) interconnected polycaprolactone/ bone fish extract scaffolds for bone tissue regeneration. Using 3D printing bone fish extract was coated on the surface of polycaprolactone scaffolds by self-assembly process. From them results it is suggested that polycaprolactone/ bone fish extract scaffolds are promising materials for use in biomedical applications to promote bone tissue regeneration.

Fish bones are a natural calcium phosphate source as postulated by Truite, et al. [85] used in biomaterial production for bone regeneration. It can be enriched with other substances' biological activity to improve bone repair. The authors used biphasic calcium phosphate (BCP) scaffolds impregnated with free curcumin (BCP-CL) or complexed with β-cyclodextrin (BCP-CD) demonstrating that curcumin impregnation in BCP scaffolds prolongs the release of the β-TCP (β-tricalcium phosphate) phase, the BCP- phase with the higher osteoinductive potential. Its finding represents an advantage in tissue engineering.

In light of Cao, et al. [86] findings, magnesium-rich calcium phosphate bioceramics from tilapia bone appear to be promising in biomedical applications such as fabricating tissue engineering scaffolds.

After a while, the study of N'deh, et al. [87] showed the effects of the collagen extract of bone from *Yeonsan Ogye* Chicken. This is the rarest of world breed of poultry with a dominant gene for fibromatosis, showing entirely black fluffy head feathers, ear lobes, and pupils. Only a few farms in Korea currently breed them. The authors pointed out that dietary supplementation with collagen extract of bone from *Yeonsan Ogye* Chicken might inhibit osteoclastogenesis, stimulate osteoblastogenesis, and regulate bone metabolism.

Peng, et al. [88] isolated collagen peptide with high affinity to Ca from Pacific cod (Gadus macrocephalus) bone and proposed it's as suggested that calcium-binding bone collagen peptide could improve the bioavailability of Ca and thus prevented Ca deficiency. Elango, et al. [60] on the other hand, had concluded that collagen peptides from *Mahi mahi* (warm water fish) bones, which have excellent osteogenic properties could be a suitable biomaterial for bone therapeutic application.

Furthermore, Seki, et al. [14] identifying ingredients associated with the prevention of osteoporosis in chicken bone and vegetable broth, concluded that hyaluronan and chondroitin sulfate present in the broth are key substances that prevent the progression of osteoporosis.

Other studies have shown that the collagen present in the broth can help reduce inflammation and improve joint elasticity, in addition, its mineral content is crucial for the body's metabolic balance [29].

Campbell-McBride [89] in the book Gut and Psychology Syndrome: Natural Treatment for Autism, Dyspraxia, A.D.D., Dyslexia, A.D.H.D., Depression, Schizophrenia, has made bone and meat broth the basis of the GAPS (Gut and Gut Syndrome psychology/physiology) protocol, due to its ability to heal and seal the intestinal lining and reduce the overgrowth of harmful microbes. Meat broth is made by cooking animal connective tissues in water, creating a healing remedy for the damaged intestinal wall of food protein-induced enterocolitis syndrome patients. The more meat broth patients consume daily, the faster they heal [89-91].

Due to its high nutrient content, anti-inflammatory properties are attributed to bone broth and its effect has been studied in a murine model of ulcerative colitis (UC). UC strictly affects the mucosa of the large intestine and rectum; its standard treatment is taking anti-inflammatories, immunosuppressants and/or colectomy [92].

In recent years, therapies based on a nutritional approach have been shown to be effective for the treatment of chronic diseases [93]. Studies carried out in murine models of colitis have shown that supplementation with amino acids and minerals can help the recovery of the gastrointestinal tract [94]. A limitation for these treatments is the high cost of supplements based on minerals and pure amino acids, which is why they are not a profitable alternative and which is why foods that provide a wide variety of minerals have been sought, among these foods is the broth of bones [18].

Mar [18] evaluated the anti-inflammatory properties of bone broth in mice with ulcerative colitis, induced through intrarectal administration of 2 mg of 2,4,6-trinitrobenzene-sulfonic acid (TNBS) dissolved in 4% acetic acid (AcOH). Results shown that the administration of bone broth as a preventive treatment decreased the damage caused by intrarectal inoculation of TNBS and AcOH, modulating the immune response by significantly reducing the expression of pro-inflammatory cytokines and increasing the expression of anti-inflammatory cytokines. These results indicate that bone broth could be an efficient and low-cost treatment for the management of ulcerative colitis.

Xing, et al. [73] also conclude from this studies that the effect of bovine bone gelatin peptides could attenuate induced colitis on dextran sodium sulfate (DSS)-induced C57BL/6 mice by suppressing the inflammatory cytokines and regulating the gut microbiota.

Homemade beef broth and soup are a staple in the GAPS diet because it provides gelatin, amino acids, fat-soluble vitamins, minerals, and all other elements necessary to reduce intestinal inflammation [95]. The intestinal mucosa contains connective tissue that plays a crucial role in the proliferation and differentiation of intestinal epithelial cells [96] and therefore acts as a key feature in intestinal barrier functions.

Basic principle of GAPS diet is based on the need for a healthy gut microbiome for human metabolic health [97]. In a study carried out by Planckaert, et al. [98] the story of seven children who recovered from food protein-induced enterocolitis syndrome (FPIES) and one child who recovered from food protein-induced allergic proctocolitis (FPIAP) after having followed the GAPS Nutritional Protocol developed by Dr. Campbell [99].

Wu, et al. [100] have pointed out that chondroitin sulfate from Sturgeon could inhibit the proliferation of the human colon cancer. Authors postulated it as a promising agent against colon cancer.

Iosageanu, et al. [101] and Iosageanu, et al. [102] have confirmed fish bone bioactive peptide's ability to control the antioxidant, anti-inflammatory, and pigmentation processes developed during UV irradiation of skin cells and recommend their use as a valuable natural ingredient of photoprotective cosmeceutical products. Authors concluded its applications in skin tissue engineering, but also in the biomedical and cosmetic fields.

Previous results of Song, et al. [103] indicated that oral administration of collagen peptides from bovine bone or proline can improve the laxity of chronologically aged skin by changing skin collagen quantitatively and qualitatively, and highlight their potential application as functional foods to combat skin aging in the chronologically aged process.

Wang, et al. [55]; Wang, et al. [104] and Yuan, et al. [105] demonstrated that bone soup nanoparticles improve the membrane potential and mitochondrial metabolism under the challenges of dihydrochloride (AAPH) free radicals, due to the antioxidant activity at the extracellular and intracellular levels of the peptides porcine bone collagen hydrolysates.

Like any typical food system, bone soup (or broth), a traditional nourishing food in many cultures, contains a colloid dispersion of self-assembled micro/nano-particles (MNPs) [69]. Colloidal micro/nano-particles (MNPs) are self-assembled particles that are found in many foods, including bone soup, coffee, tea, fruit, and herbal decoctions. They are formed during food processing through chemical reactions and physical interactions [106].

Xu, et al. [66] pointed out that fish collagen peptides have biological activities such as antioxidant, antibacterial, antitumor, immunomodulatory, and hypoglycemic, and they are widely used in medicinal applications. Although collagen peptides have efficacy in preventing and treating various diseases, further research and clinical trials are still needed to improve the utilization value.

Moreover, the bone broth is effective in preventing and treating inflammatory bowel disease and poor functioning of the immune system, thanks to the collagen that it contains. Collagen contains glycine and arginine among its amino acids which are known for their anti-inflammatory properties, this means that it has potential as a dietary treatment for intestinal disorders by restoring intestinal barrier dysfunction and reducing paracellular permeability generated by oxidative stress [10].

Glycosaminoglycans (GAGs) are responsible for preserving the hardness of bone tissue, as well as regulating collagen formation and mineralization in the extracellular matrix [107]. GAGs are not the only component of broth that improves joint health. Collagen can also benefit joints. In one study, researchers found that athletes experienced less joint pain after taking collagen supplements. A combination of chondroitin sulfate and glucosamine can be used to partially treat osteoarthritis, Cartilage from animals, such as cow, pig or shark, is most frequently chosen as raw material to extract chondroitin sulfate and in addition to cartilage, another resource can be chicken leg bone. There are studies that confirm that broth chicken leg bones are a source of chondroitin sulfate [108]. On the other hand, Inacio, et al. [109] review supports the potential of collagen peptide supplementation to mitigate muscle stress from acute strenuous resistance training.

The results reported by Cao, et al. [110] suggest that chicken bone collagen peptides, prepared from chicken bone by enzymatic hydrolysis, and administered orally might be used as a functional anti-aging nutritional component. Moreover, notably, collagen supplements enriched with essential amino acids such as proline and glycine, along with marine fish collagen, have become popular for their safety and effectiveness in mitigating the aging process [111].

Later the studies of Zhang, et al. [112] on aging mice, pointed out that collagen peptide can improve skin problems caused by aging, promote skin hydration and antioxidant capacity, and regulate collagen synthesis and degradation through the mitogen-activated protein kinase pathway.

Hwang, et al. [113] have studied the effects of the collagen peptides extracted from the scales of Mozambique tilapia (*Oreochromis mossambicus*) to promote hair and skin health. The results indicate that collagen peptides

extracted could be used as food supplements and nutraceuticals for hair loss prevention as well as hair regrowth during alopecia.

Bovine bone collagen oligopeptides (BCOP) could be an alternative effective wound healing in mice as reported by Li, et al. [114]; Li, et al. [115] and Li, et al. [116] whom pointed out that oral administration of BCOP could promote wound healing in mice.

Bone broth is a beneficial option for cancer patients, it can help overcome the side effects of treatment such as lack of appetite, nausea, and the amino acids present help calm intestinal irritation and inflammation [117].

Bone broth contains glucosamine which may help stop progression in several types of cancer [114, 118, 119] however, the impact of glucosamine supplementation on cancer mortality remains unclear. Studies suggest that the regular use of glucosamine may have different functions in the risk of different types of cancer, but not in all; in the specific case of lung cancer, the consumption of glucosamine reduces the risk of suffering from it by 16% [120, 121].

Bone marrow fat tissue secretes hormones that help the body stay healthy, the University of Michigan-led study shows that the fat tissue in bone marrow is a significant source of the hormone adiponectin, which helps maintain insulin sensitivity, break down fat, and has been linked to decreased risk of cardiovascular disease, diabetes, and obesity- associated cancers [122].

Choi, et al. [123] demonstrate that water extract of deer bone called called nok-gol in Korean helpful for alleviating neutropenia (low white blood cells, specifically neutrophils).

## 8. CONCLUSION

As a traditional food; bone broth is consumed around the world not only for nutrition, but also for its properties of preventing and treating inflammatory bowel diseases (IBD) and improving the immune system, among others. Through prolonged cooking of animal bones, such as beef, pork, chicken, and others animal a variety of essential nutrients are extracted; such, as calcium, iron and magnesium, as well as amino acids that are essential for various biological functions in the human body. This review compiles information on the health benefits of bone broth, which can be particularly beneficial for consumers with special dietary regimes.

To maximize the extraction of nutrients in bone broth, several factors must be considered, such as the choice of bone type, cooking time, and temperature, as well as the addition of acidic ingredients such as vinegar or lemon juice, to facilitate the dissolution of the minerals present in the bones, increasing their bioavailability. Moreover, alternative preparation methods, such as freeze-drying or agent extractors, can further increase the quantity and quality of nutrients available in the final product.

In summary, the most relevant contributions to the health of bone broth extract are its ability to improve digestive health, strengthen the immune system, and contribute to bone health; emphasizing the control of Diabetes, colitis, antiaging, skin healing, and alopecia, among others. The confirmation of these results can open new market areas for broth extract use in food applications or to production of new supplements. Furthermore, provides a solution for waste byproducts from meat, poultry, and fish industries, due to the added value to the process.

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