Heliyon 10 (2024) e40563

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Bioactive peptides from food science to pharmaceutical industries: Their mechanism of action, potential role in cancer treatment and available resources

Maryam Bidram, Mohamad Reza Ganjalikhany *

Department of Cell and Molecular Biology, Faculty of Biological Science and Technology, University of Isfahan, Isfahan, Iran

ARTICLE INFO

Keywords:
Bioactive peptides
Cancer
Therapeutic applications
Anticancer peptides
Functional foods
Natural resources

ABSTRACT

Cancer is known as the main cause of mortality in the world, and every year, the rate of incidence and death due to cancer is increasing. Bioactive peptides are one of the novel therapeutic options that are considered a suitable alternative to toxic chemotherapy drugs because they limit side effects with their specific function. In fact, bioactive peptides are short amino acid sequences that obtain diverse physiological functions to maintain human health after being released from parent proteins. This group of biological molecules that can be isolated from different types of natural protein sources has attracted much attention in the field of pharmaceutical and functional foods production. The current article describes the therapeutic benefits of bioactive peptides and specifically and extensively reviews their role in cancer treatment, available sources for discovering anticancer peptides, mechanisms of action, production methods, and existing challenges.

1. Introduction

Health and high quality of life are the most valuable assets of a society, and they are pivotal for having a happy, economically active, and productive society. Fostering healthy lifestyle behaviors including a proper diet containing nutritious factors and bioactive compounds, adequate sleep, and physical activities are essential for the primary prevention of cancer [1,2]. Cancer is considered the leading lethal cause and an important obstacle to increasing the life expectancy of people worldwide. Its growing trend is predicted in the coming years, with an estimated 13.2 million deaths in 2030 [3]. Therefore, cancer is a serious threat to health, and combating it is one of the important goals to increase the quality of human life. Chemotherapy, radiation therapy, and surgery are conventional methods for cancer treatment, which are used individually or in combination depending on the type and stage of cancer [4]. Despite the medicinal advancements in recent years, these methods are associated with problems, the most important of which include the lack of specificity to the cancer target and the development of cancer cells' resistance to these drugs. The inability of these methods to distinguish between normal and cancer cells leads to toxicity and damage to normal cells along with cancer cells. Therefore, adverse and severe side effects, as well as multidrug resistance due to long-term usage are the main obstacles to the treatment of this disease [5,6].

Consequently, it has become a challenge for researchers to identify new effective therapeutic agents that specifically affect the eradication of cancer cells and improve patients' treatment satisfaction. In recent years, peptides have been considered suitable drug candidates due to their numerous advantages, including small size, target specificity, and low toxicity, and they have been developed

* Corresponding author.
E-mail address: m.ganjalikhany@sci.ui.ac.ir (M.R. Ganjalikhany).

https://doi.org/10.1016/j.heliyon.2024.e40563
Received 8 February 2024; Received in revised form 29 October 2024; Accepted 19 November 2024
Available online 22 November 2024

to treat many diseases, such as cancer [7]. To date, more than 80 peptide drugs have been approved by the FDA (Food and Drug Administration) and entered the market, and many others are in the pre-clinical and clinical stages [8]. Peptide-based drugs or anticancer peptides exert their oncolytic effects through different mechanisms. They bind to cell surface proteins, followed by internalization into the target cell or direct passage through the membrane [9]. One of the common strategies to discover anticancer peptides is to purify and identify them from natural sources. These peptides, known as bioactive peptides or cryptides, are inactive amino acid sequences buried in the structure of the parent proteins, which exhibit various biological activities after being released [10]. They exist in two forms: peptides produced in different cells and glands of the body are known as endogenous, and peptides that enter the body through foods and medications are referred to as exogenous peptides [11]. Bioactive peptides usually have a length between 2 and 50 residues, and this small size is an advantage over other biological drugs, such as antibodies and proteins, for therapeutic applications because, in addition to facilitating their passage through blood vessels, they are less allergenic. Moreover, timely and easy destruction after consumption and body clearance without accumulation is another desirable feature of bioactive peptides compared to synthetic drugs [12,13]. Bioactive peptides have increased interest because of their diverse physiological activities. In the realm of cancer therapy, bioactive peptides have received attention due to their ability to induce cell death, especially through apoptosis, which is the most common strategy to reduce the proliferation of cancer cells. Also, bioactive peptides operate as a tool for immune modulation by stimulating or suppressing the immune responses, and by activating immune cells and cytokines, they can promote a robust defense barrier against cancer cells. Inhibition of angiogenesis and suppression of migration are other anticancer effects of bioactive peptides [14]. Considering the identification of bioactive peptides as a new generation of biologically active regulators and their role in improving health outcomes, this review scope presents the anticancer properties and mechanisms of action of bioactive peptides, various sources, production methods, and existing challenges.

2. Sources of anticancer bioactive peptides

Generally, bioactive peptides can be isolated from any organism, including various animal and plant protein sources and microorganisms. However, choosing a target source with a high content of protein and bioactive peptides makes the purification process more affordable [15]. Romidepsin is a histone deacetylase (HDAC) inhibitor isolated from the bacterium *Chromobacterium violaceum*. Romidepsin, which is known as a depsipeptide, exerts its antitumor effects by blocking the action of histone deacetylase enzymes, especially class I, and also by modulating factors influential in cancer, including c-myc, Hsp90, and p53. This FDA-approved cyclopeptide is an anticancer agent to treat patients with cutaneous T-cell lymphoma (CTCL) [16,17]. In the following, further descriptions of these sources will be addressed.

2.1. Animal sources

So far, many animal protein sources, including marine animals (types of fish, shrimp, sponges, oysters, tunicates), terrestrial animals, Insects, amphibians, milk and dairy products, eggs, meat, bovine blood, and animal venoms, have been used to produce bioactive peptides [18]. Some of them will be mentioned below.

As the largest biome in the world, the marine biome covers 70 % of the earth's surface and is a manifestation of abundant, untouched, or underexploited natural resources. The marine biome is the habitat of about 10 million different plant and animal species, and this massive biodiversity compared to the land surface creates a new impetus to meet the growing ecological, and socioeconomic needs [19]. Therefore, the marine biome constitutes an acceptable and rich natural source of new compounds with superior performance, which can be used especially for the discovery of valuable bioactive peptides. Easy access to these sources and biological products derived from them, as well as high efficiency and low side effects compared to similar synthetic examples, are among its advantages. Harsh and extreme conditions in the marine biome, such as darkness, low temperature, salinity, UV exposure, high pressure, and limited food, force marine organisms/microorganisms to adapt to existing conditions to survive [20]. The production of stable metabolites and more effective bioactive compounds for rapid adaptation to new environmental conditions has made them a valuable resource. Marine resources, especially microorganisms such as microalgae, are a suitable choice for the production of proteins and therapeutic peptides due to their high protein content [21]. However, due to the lack of access to the deeper areas of the marine biome, there are still unknown bioactive peptides. Peptides extracted from marine sources lead to the death of cancer cells through different strategies including induction of apoptosis, antiproliferative/cytotoxic activities, suppression of angiogenesis, and regulation of tubulin–microtubule balance [22]. Many peptides with antitumor function against cancerous cells have been identified from marine sources; some are currently in different phases of clinical trials, and some are commercialized. For example, aplidine is a depsipeptide with a cyclic structure obtained from the Mediterranean tunicate *Aplidium albicans* and is now a commercially available product. *In vitro* and *in vivo* studies conducted to evaluate the effect of aplidine in cancer have shown its significant role in causing toxicity against various cancer cells [23,24]. Broggini et al. have indicated that treatment of MOLT-4 leukemia cells with aplidine inhibited the secretion of VEGF by these cells and blocked their binding with VEGFR1 on the cell surface. Therefore, aplidine, as an anticancer product of marine origin, reduces tumor growth and induces cell death [25]. Furthermore, the peptide AATP with the sequence KVEPQDPSEW has been purified from the abalone (*Haliotis discus hannai*), which has led to a remarkable inhibition in the migration and invasion processes of HT-1080 cells by reducing the effective factors in angiogenesis such as VEGF and MMPs [26].

Terrestrial mammals can also be used to produce bioactive peptides; beef, pork, goat liver, and spleen are examples of this category. In this regard, anticancer bioactive peptide (ACBP) was identified from goat spleens, and its inhibitory effect on the growth of the human gastric cancer cell line (BGC-823) was confirmed *in vitro* and *in vivo*. Morphological changes caused by peptide-induced apoptosis and cell cycle arrest, as well as increased expression of pro-apoptotic and tumor-suppressing genes and decreased tumor-

promoting genes at the molecular level, have been observed in ACBP-treated cancer cells [27]. Moreover, the significant role of ACBPs in inhibiting the growth and proliferation of tumor cells in various other cancers such as leukemia, colorectal, gallbladder, and nasopharyngeal has been investigated and validated by this group [28–31]. Investigations conducted on the peptide fraction of *Musca domestica* larvae (MDPF) have shown a decrease in mouse S180 sarcoma growth and an increase in the proliferation of splenocytes and cytokines produced from them, enhancement of natural killer cells and cytotoxic T lymphocytes activity, and promotion of the level of antigen-specific antibodies. Therefore, the observed results have introduced MDPF as an antitumor agent with immune system improvement activity [32]. Dermaseptins B2 and B3, two peptides isolated from South American tree frog (*Phyllomedusa bicolor*) skin secretions, have shown anti-proliferative and angiostatic activities. According to the report of van Zoggel et al., treatment with these two peptides has led to inhibiting the proliferation of human prostate cancer (PC-3) cells [33]. Other types of peptides of this family, including dermaseptin-PD-1 and dermaseptin-PD-2 found in giant mexican leaf frog (*Pachymedusa dacnicolor*) skin secretions [34] and dermaseptin L1 obtained from lemur frog (*Agalychnis lemur*) skin secretions [35], have also indicated anticancer properties against various tumor cells. The investigation of a hexapeptide (PGPIPN) isolated from bovine milk beta-casein by Zhao et al. on ovarian cancer cells has shown inhibition of invasion and metastasis in a dose-dependent manner so that the studied peptide has reduced the expression of MTA1 and NM23H1 as effective genes in these two critical pathways of tumor progression [36]. In addition to the studies conducted on animal milk, Chiangjong et al. discovered a new peptide (HMP-S7) from human breast milk, which demonstrated a cytotoxic effect on several leukemia cell lines without affecting normal cells [37]. Ovotransferrin (OTF), with an amount of 12 %, is one of the most abundant proteins in egg white after ovalbumin (54 %), and various biological activities of this protein and peptides resulting from its hydrolysis have been reported [38]. In one study, the hydrolysates produced from the hydrolysis of ovotransferrin with promod 278P and thermolysin enzymes have shown antioxidant and anticancer properties. In fact, by enzymatic hydrolysis and enhancing its bioactivity, these hydrolysates have indicated stronger cytotoxic effects compared to intact ovotransferrin on AGS, LoVo, HT-29, and HeLa human cancer cell lines [39]. Crotamine is a cationic polypeptide derived from South American rattlesnake *Crotalus durissus terrificus* venom, which is considered one of the cell-penetrating (CPP) and antimicrobial (AMP) peptides. Studies conducted on this peptide demonstrate that in addition to antimicrobial and antifungal activities, it has cytotoxic effects on tumor tissues. The high specificity of crotamine to proliferating cells and its transfer into the cell targets organelles such as the lysosomes and causes the release of its contents and the activation of proteases, thus inducing toxicity and cell death through this mechanism [40,41].

2.2. Plant sources

Plants have been considered a primary source of natural medicines since ancient times, and due to their significant capabilities in treatment, many plant extracts have been used in cancer research. Among the screened plant species, more than 3000 plants have demonstrated anticancer activity [42]. Bioactive peptides can be isolated from diverse plant species, both edible and non-edible. An example in this field is the anticancer peptide obtained from *Gynura pseudochina* named Gynurin, which in the dimer form of LNCCNLLL resulting from the formation of disulfide bonds has led to the inhibition of growth and proliferation of human gastric cancer cell line (KATO-III) without any effect on normal cells [43]. The main plant sources for the purification of biologically active peptides that are consumed as food include fruits and vegetables, grains, and legumes. In general, an advantage of these sources compared to animal sources is the lack of prejudice towards their use, so they are readily accepted as raw materials for extracting protein and bioactive compounds [44]. Ma et al. have evaluated defatted walnut (*Juglans regia* L.) protein hydrolysates for the presence of anticancer peptides. The results have shown the identification of CTLEW as a peptide with anticancer properties from this plant source. In this study, the walnut residual protein after defatting has been subjected to hydrolysis with five enzymes, and the mentioned purified peptide has led to inhibiting the growth of breast cancer MCF-7 cells by increasing apoptosis and autophagy; in addition, it has been effective in reducing the growth of Caco-2 and HeLa cells [45]. Bitter gourd (*Momordica charantia*) contains many phytochemicals that lead to antidiabetic, anticancer, antimicrobial, antioxidant, and antihypertensive properties. BG-4 is a peptide derived from bitter gourd seeds and has been found to have an inhibitory activity on colon cancer cells by affecting proteins involved in apoptosis and cell cycle [46]. The evaluation of corn-derived peptides for anticancer function has shown a decrease in the survival of liver hepatocellular carcinoma cells (HepG2) by inducing cell death, cell cycle arrest, and boosting the immune system [47]. In another study, rice bran has been used as a source for the purification of antitumor peptides, and the fraction containing peptides with a molecular weight below 5 kDa has led to the inhibition of cancer cells proliferation. Pentapeptide Glu-Gln-Arg-Pro-Arg with anticancer properties has been identified from this fraction through mass spectrometry analysis and *de novo* sequencing [48]. Studies conducted on kafirin as the main and abundant protein stored in sorghum have confirmed its anticancer effect. The kafirin hydrolysates produced with papain enzyme have shown a significant reduction in the growth of HepG2 cancer cells [49]. *Salvia hispanica* (chia) is a pseudocereal with high protein content, which Quintal-Bojórquez et al. found that its protein fractions have an anticancer effect on MCF-7, Caco2, PC-3, and HepG2 cell lines. The peptide KLKKNL has been sequenced from one of the protein fractions with the highest efficiency [50]. In the case of legumes, two antimicrobial peptides, lunatusin and vulgarinin, both with a molecular weight of 7.0 kDa, have been identified from Chinese lima bean (*Phaseolus lunatus* L.) and haricot beans (*Phaseolus vulgaris*), respectively, which show almost similar antibacterial and antifungal function. Two peptides have also exerted anticancer activity on tumor cells, such that lunatusin prevented the proliferation of breast cancer cell line (MCF-7) and vulgarinin from leukemia (L1210 and M1) and breast (MCF-7) cell lines [51,52].

Given the estimated population of 9 billion by 2050 and concerns about meeting food needs, marine algae have attracted much attention in the food industry due to their high protein content, which exceeds even other protein sources such as milk and soybean. Algae, as a source of bioactive compounds, have shown many health-promoting effects, including anticancer activity [53,54]. The antiproliferative effect of the peptides obtained from the enzymatic hydrolysis of *Porphyra haitanesis* seaweed protein has been investigated on five cell lines from breast, liver, gastric, lung, and colon cancer, and finally, the purified peptide with sequence

VPGTPKNLDSPR has inhibited the proliferation of MCF-7 cells by preventing the cell cycle and inducing apoptosis [55]. Microalgae are photosynthetic microorganisms that, like macroalgae, are considered a rich source of nutrients and anti-cancerous bioactive compounds. Ko et al. have identified heptapeptide Leu-Leu-Ala-Pro-Pro-Glu-Arg from microalgae *Pavlova lutheri*, which inhibits MMP-9 production in PMA-stimulated HT-1080 fibrosarcoma cells by interfering with the activity of JNK, p38, and NF-κB pathways [56].

2.3. Agro-industrial waste as a novel source of bioactive peptides

In many researches, expensive protein sources have been used to isolate bioactive peptides, while choosing a suitable source can play a significant role in improving the purification process and reducing production costs. Agro-industrial activities usually generate much waste, which, in addition to causing environmental problems, requires high expenses to manage and dispose of them [57]. The recent developments in the food industry are associated with challenges, the most important of which are food safety and handling by-products. Reports indicate that one-third of the food produced for humans, which is about 1.3 billion tons, according to the reports of the Food and Agricultural Organization of the United Nations (FAO), is lost or wasted every year [58]. Depending on the type of origin, waste can be divided into two categories: wastes of animal origin which are related to meat, seafood, and dairy processing industries, and waste of plant-based wastes, which are related to fruit and vegetable industries, that constitute a major volume of waste, including peels/skins, leaves, seeds, shells, pods, cores, pulp, pomace (solid waste) and juice (liquid waste). Using common methods such as incineration and landfill for waste disposal has many environmental consequences because they produce pollutants and greenhouse gases such as carbon dioxide and methane, respectively. Hence, waste management in order to reduce or convert them into nutraceutical products is one of the essential goals in performing the best processes, which requires a basic understanding of the production of food waste, the volume produced, the nature, and the characteristics of its components [59,60]. These by-products usually constitute a valuable source of proteins that can be precursors for the isolation of bioactive compounds beneficial in health, especially in developing countries that are associated with a deficiency of protein sources [61]. For example, tomato (*Solanum lycopersicum* L.) pomace, which mainly contains skin and seeds, is removed as waste material after processing this fruit into sauces, juices, puree, etc. Based on the reports, tomato seeds are rich in bioactive compounds, including proteins/peptides, vitamins, phytochemicals, lycopene, and pectin, and have antioxidant, antitumor, and antimicrobial effects [62]. Therefore, the use of these unusable and non-renewable materials, which are produced every year in large volumes by different countries, in addition to providing a significant and cheap protein source, also contributes to the sustainability of the environment and can be a suitable solution for the world population growth and people's nutrition concerns [63]. In this field, studies have been conducted so far, some of which will be mentioned below.

V'asquez-Villanueva et al. have reported an antitumor peptide with the sequence LLPSY from the fraction containing peptides with molecular weights of less than 3 kDa and the highest antihypertensive activity, which has been produced from olive seed hydrolysates with thermolysin enzyme. This peptide has shown a significant inhibitory effect on MDA-MB-468 and PC-3 cancer cell lines [64]. IbACP (AASTPVGGGRRLDRGQ) is a peptide with anticancer effects identified from sweet potato leaves (*Ipomoea batatas*). This peptide, which is sixteen amino acids long, has inhibited the Panc-1 pancreatic cancer cell line via triggering apoptosis. In addition, an augmentation in the level of cleaved caspase 3 and 9 and poly (ADP-Ribose) polymerase (PARP) activity has been observed in cells treated with IbACP [65]. Soybean is considered as one of the most widely consumed legumes in the world, which is cultivated for oil extraction in addition to its high protein content. Soybean meal is a residual by-product after extracting oil from seeds. Rayaprolu et al. have used this protein source to identify anticancer peptides against colon, lung, and liver cell lines [66]. In another study, pepsin hydrolysates from algae protein wastes have demonstrated an inhibitory effect on the growth of AGS human gastric adenocarcinoma cells. Peptide VECYGPNRPQF, with the best anti-proliferative and antioxidant performance, has been identified from the effective peptide fraction [67]. The inclusion of fish consumption in the diet is recommended due to its high benefits; however, fish processing generates a high percentage of by-products such as head, backbone, fins, viscera, and skin, which have attracted the attention of researchers to investigate biomedical properties of their components and integration into food supplements [68]. Yaghoubzadeh et al. have focused on novel peptides from fish by-products and investigated their antioxidant and anticancer activities. In this study, enzymatic hydrolysis by Flavourzyme and Alcalase and ultrafiltration method have been used to prepare bioactive peptides from rainbow trout skin (*Oncorhynchus mykiss*). The results have shown the antioxidant activity dependent on the concentration of hydrolyzed protein (Flavourzyme higher than Alcalase) and inhibition of colon cancer cells (HCT-116) growth by peptide fractions with a molecular weight of less than 3 kDa [69]. In addition, the antiproliferative potential of protein hydrolysates of Meagres "*Argirosomus Regius*" and Gilthead Sea Breams "*Sparus Aurata*" by-products has been proven on COLO320 and MCF7A cell lines [70]. Abundant cultivation of rice in order to provide the main source of food for many people produces about 120 million tons of rice husks every year, which is considered one of the major agricultural wastes. Ilhan-Ayisigi et al. have shown the anticancer effect of rice husk-derived protein hydrolysates in two forms, free and encapsulated in chitosan, on human lung cancer cell line A549 and human breast tumor cell lines MCF7 and MDA-MB–231 [71].

3. Biological functions of bioactive peptides

Bioactive peptides have great potential to regulate and treat health-related disorders; from this point of view, their antimicrobial, anti-inflammatory, antioxidant, antidiabetic, antihypertensive, lowering blood cholesterol, opioid, immunoregulatory, mineral-binding, antiobesity, and anticancer therapeutic properties can be mentioned (Fig. 1). The characteristics of these biological functions are often dependent on the properties of the peptide, including chain length, molecular weight, amino acid composition,

conformation, net charge, and hydrophobicity [72].

According to statistics, 5 % of the main functions of antimicrobial peptides are related to anticancer activities. In other words, some antimicrobial peptides, in addition to their capabilities to eliminate microorganisms and protect the host against infectious agents, are able to induce toxicity in cancer cells through membrane targeting mechanisms (or other mechanisms) and are generally known as anticancer peptides (ACPs) [73]. Porcine cathelicidin peptide, tritrpticin (VRRFPWWWPFLRR), and its derivatives, including indolicidin and puroindoline A, have exhibited significant toxicity in the Jurkat T cell leukemia line. The selectivity of these peptides has been increased by substituting arginine with lysine. Accordingly, the insertion of cationic amino acids based on lysine can be a suitable approach to improve the selectivity of synthetic anticancer peptides [74]. Considering the promising results related to the role of antimicrobial peptides in cancer treatment and the existence of limited information about their mechanisms of action, further research in this area could highlight their importance in the food and pharmaceutical industries. Chronic inflammation caused by not removing inflammatory factors increases the risk of diseases, including cancer, so it is considered as a carcinogenic factor [75]. By reducing and inhibiting pro-inflammatory mediators, bioactive peptides protect the organism from the adverse effects of excessive inflammatory response. For example, Cruz-Chamorro et al. have shown the anti-inflammatory effect of two peptides, WVSPLAGRT and IGFLIIWV, purified from the hydrolysates of hempseed [76]. Oxidative stress conditions also provide an opportunity for diseases such as cancer by causing serious damage to cellular components such as DNA, lipids, and proteins. In a study, in order to effectively use by-products of monkfish (*Lophius litulon*) processing, monkfish swim bladders proteins were hydrolyzed by papain protease, and the antioxidant activity of 18 identified peptides was evaluated and determined [77]. The development of immunoregulatory bioactive peptides to better control diseases such as cancer by the immune system can be a suitable alternative to therapeutic agents [78]. These peptides help to regulate the immune system through immune stimulation or immunosuppression; therefore, in addition to improving immunity, they are also useful in conditions such as autoimmune diseases. The mechanism of action of immune regulatory peptides is different in the way that they affect the toxicity of natural killer (NK) cells, phagocytic activity of macrophages, proliferation or removal of lymphocytes, secretion of cytokines from T lymphocytes, and antibody production from B lymphocytes [79]. PEP1 peptide with amino acid sequence GIAASPFLQSAAFQLR obtained from rice (*Oryza sativa* L.) protein has been identified as an immunopeptide [80].

3.1. Anticancer activity

3.1.1. Overview of cancer

According to a cross-continental study conducted in 21 countries, it has been observed that cancer is the principal cause of mortality in many countries [81]. Based on the International Agency for Research on Cancer (IARC) statistics, in 2022, close to 20 million new cases of cancer and 9.7 million deaths are estimated worldwide, and by 2050 the number of new cases is expected to reach 35 million, highlighting the growing global burden of cancer. The findings show that one in five people develop cancer during their lifetime and almost 1 in 9 men and 1 in 12 women die as a result of this disease. Lung cancer is diagnosed as the most common cancer

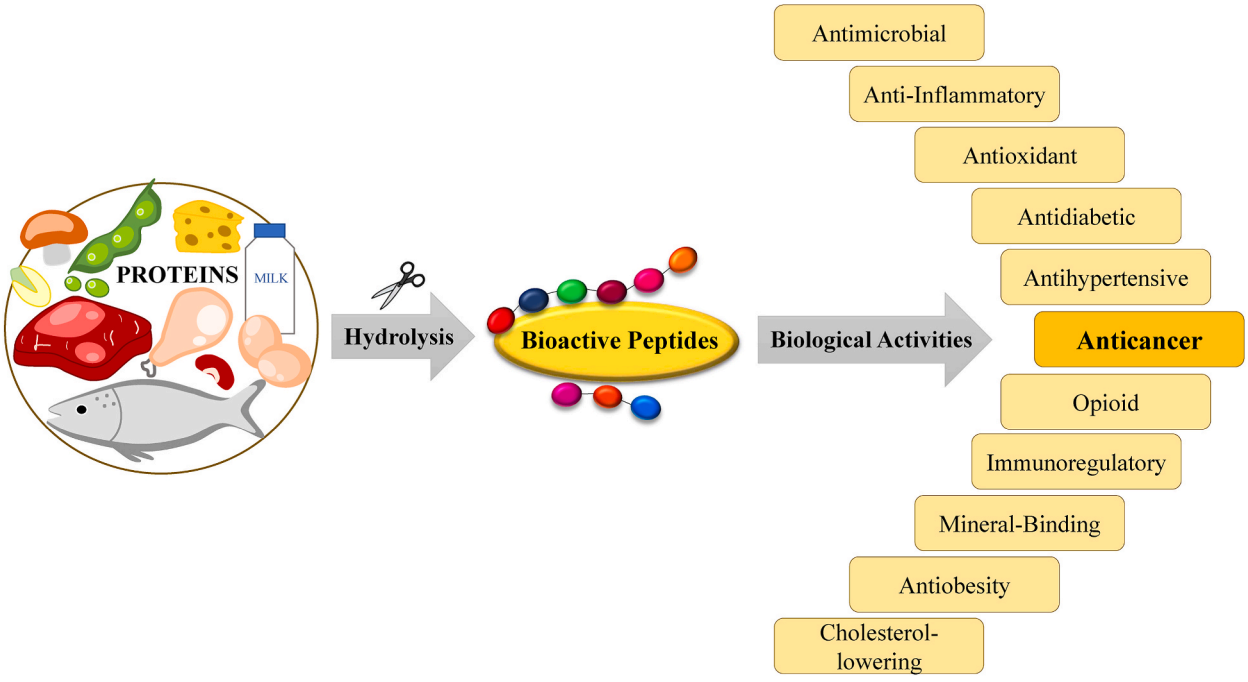

Fig. 1. Discovery of bioactive peptides from various sources with the potential to perform several biological activities in the body.

with 2.5 million new cases identified in 2022, accounting for 12.4 % of all cancers globally. Moreover, lung cancer is the deadliest cancer and leading cause of mortality in the world with 1.8 million deaths or 1 in 5 deaths [82]. Among the cases of lung cancer, non-small-cell lung cancer (NSCLC) accounts for about 85 % and small-cell lung cancer (SCLC) for 15 % of the rest, and in general, in most cases, the main cause of the disease is the entry of toxic substances into the lungs through smoking [83]. The next most common cancers reported include breast (2.3 million new cases, 11.6 %), colorectal (1.9 million new cases, 9.6 %), and prostate (1.5 million new cases, 7.3 %) respectively, among which, based on gender differences, lung cancer in men and breast cancer (666,000 deaths) in women are the most frequent cancers in terms of incidence and mortality [82]. Colorectal cancer, as the second cause of cancer-related deaths (904,000 deaths), usually begins with the formation of pre-cancerous polyps in the inner wall of the colon or rectum. Although there are different types of colorectal cancers, adenocarcinomas are the most common types that form in mucus-producing cells [84]. Prostate cancer with 397,000 deaths worldwide, is specific and common in men. Since this exocrine gland performs important functions in the body, people with this type of cancer may experience various problems in urination, ejaculation, and fertility [85]. Melanoma is the most aggressive and deadly type of skin cancer that starts in the pigment-producing cells or melanocytes. Malignant melanoma is responsible for the death of approximately 58,667 people due to its high development and progression speed and ability to invade and spread to other organs [86]. Cancers can be treated if diagnosed in time, and in the early stages of the disease, but advanced cancers reduce the chance of survival due to metastasis to distant organs. There are many factors that directly or indirectly contribute to the development of cancer, which makes the treatment of cancer complicated and, in some cases, impossible. Chemotherapy is considered the most effective and extensively used method for cancer treatment, and in recent years, advances in chemotherapy drugs, as well as the development of new strategies such as targeted therapy, stem cell therapy, and nanoparticles, along with conventional strategies, have played a significant role in the recovery of patients. Chemotherapy drugs usually prevent the growth and proliferation of cancer cells by increasing reactive oxygen species (ROS) and inducing apoptosis (programmed cell death) [87,88]. However, due to the lack of specificity to cancer cells, chemical drugs also affect normal cells. As a result, they are associated with side effects such as nausea, hair loss, and immunodeficiency, which makes their use a worrisome issue [89]. Therefore, the emphasis on identifying anticancer approaches with no or low side effects has led researchers to search for novel biological molecules instead of harmful chemical drugs.

3.1.2. Anticancer bioactive peptides

Bioactive peptides, as small biological molecules derived from protein sources, can be used in cancer treatment because their cytotoxic activity against different cancer cell lines has been proven. Actually, peptides represent their anticancer function with various mechanisms (Fig. 2) and limited side effects. In addition to the function of peptides as cytotoxic compounds, they also have the potential to be used as carriers for toxic agents, which increases their application capabilities. Bioactive peptides also reduce the high treatment costs caused by chemotherapy and minimize tissue damage with specific functions, so they can be considered a suitable option for the treatment of this metabolic disease and an alternative to conventional methods [90,91].

Since growing tumors perform angiogenesis to supply oxygen and nutrients, and the formation of these new vessels is one of the

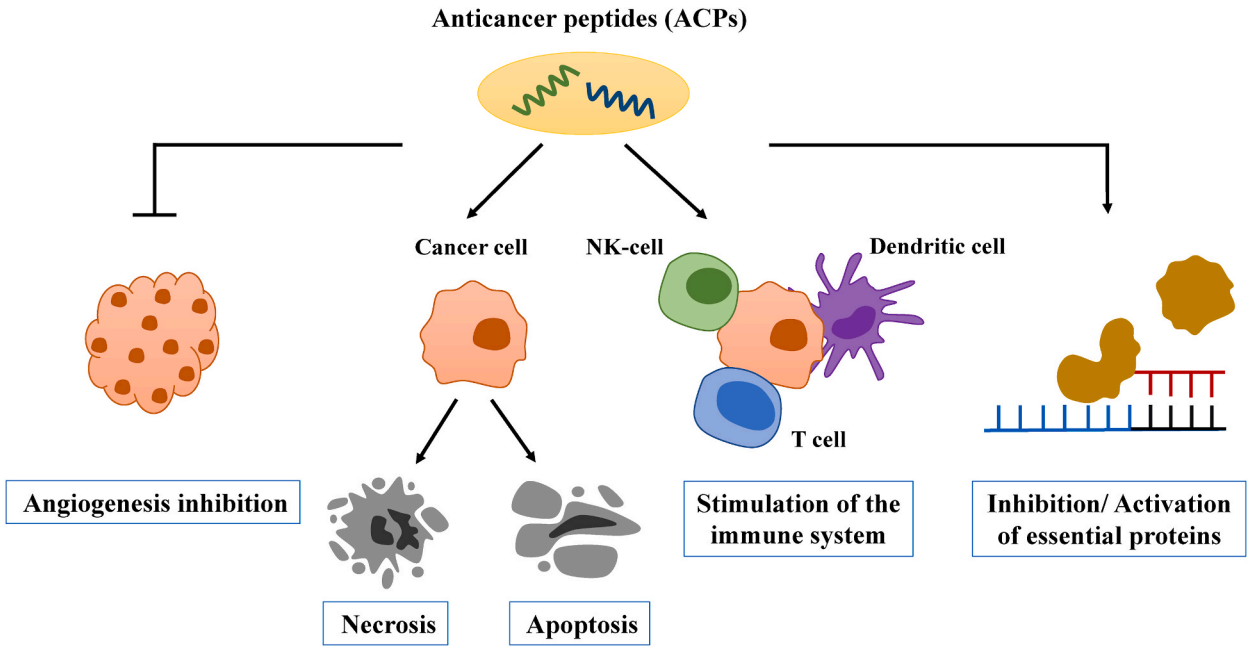

Fig. 2. Different strategies of anticancer peptides (ACPs) to attack cancer cells. The modes of action of ACPs include inhibiting the angiogenesis process, cancer cell death through apoptosis or necrosis, stimulation of the immune system, or affecting essential proteins. Various ACPs may employ more than one strategy.

main effective factors in metastasis, inhibition of angiogenesis plays a significant role in cancer treatment, so this process is one of the targets of anticancer drugs [92]. Bioactive peptides also inhibit angiogenesis, which is one of their anticancer strategies. For example, a peptide purified from shark cartilage has shown anti-angiogenic effects in the zebrafish embryos model. Moreover, inhibition of VEGF-mediated migration and tubulogenesis in human umbilical vein endothelial cells (HUVECs) was achieved by this peptide in a dose-dependent manner [93]. Vascular endothelial growth factor (VEGFs) family members and their receptors (VEGFRs) are the important regulators of angiogenesis, among which VEGFA and VEGFR2 play the main role. Ligand binding to cell surface receptors initiates the signaling cascades of cell proliferation, migration, survival, and, finally, angiogenesis [94]. As a result, they are a good target for therapeutic agents. Liu et al. confirmed the anti-angiogenic effect of CS5931 polypeptide isolated from *Ciona savignyi* through the inhibition of VEGF and matrix metalloproteinases (MMP-2 and MMP-9) expression *in vitro* and *in vivo* and introduced it as an agent in cancer treatment [95]. Furthermore, aplidine, a known cyclodepsipeptide from marine origin, has shown significant potential in inhibiting angiogenesis and as an anticancer compound [24].

Another strategy used by anticancer peptides is the induction of cell death through pathways such as apoptosis and necrosis. Since escaping from apoptosis is one of the characteristics of cancer cells, understanding this pathway and the proteins involved in it can be helpful in eliminating cancer cells [96]. Apoptosis takes place through two pathways: the extrinsic pathway starts with the binding of ligands to death receptors, such as the binding of TNF to TNFR1, and the intrinsic pathway increases mitochondrial membrane permeability by stimuli such as oncogenes [97]. The increase or decrease of pro-apoptotic and anti-apoptotic proteins are involved in this process; it will be discussed in detail below. So far, many bioactive peptides from different sources have been reported to exert their anticancer effects by activating apoptosis. For example, it has been shown that a peptide originating from ginger has the ability to increase apoptosis in leukemia cells. This peptide (RALGWSCL), which was isolated from the fraction with the highest toxicity, led to the upregulation of caspases 3, 8, and 9 and the pro-apoptotic protein BAX, and the downregulation of the anti-apoptotic protein BCL2. Furthermore, the treatment of cancer cells with the resulting peptide has demonstrated an increase in the expression of P53 at the level of mRNA and protein as the key regulator in apoptosis [98]. The peptide lunasin, which was first detected in soy and then in other grains, has shown its efficacy in cancer prevention and treatment by suppressing mitosis and cell proliferation and increasing cell death in many *in vitro* and *in vivo* experiments [99]. For instance, to evaluate the protective role of lunasin in breast cancer, mice fed with a diet containing 0.23 % lunasin showed a decrease in tumor occurrence from 67 % to 50 % compared to the control group [100]. Since maize is the most widely consumed cereal in the world, many studies have used cellular experiments to evaluate its anticancer effect [101]. Ortiz-Martinez et al. have indicated the antiproliferative property of maize-derived peptide fractions on HepG2 human hepatocarcinoma cells, which probably act by reducing the expression of anti-apoptotic factors and inducing apoptosis [102]. In general, food proteins are considered a valuable source for the discovery of anticancer peptides. In 2019, the investigation of regular consumption of kefir (fermented milk) on the incidence of pre-neoplastic colonic lesions in Wistar rats was carried out. The results have revealed a decrease in the observation of abnormal crypt foci (ACF), an increase in the production of short-chain fatty acids, as well as an elevation in the concentration of TNF-α and IL-1β, and the enzyme catalase in the colon carcinogenetic model [103].

Furthermore, bioactive peptides block intermediates in the signaling pathways related to cell growth and proliferation, for example, through deformation and inactivation of enzymes. Also, boosting the immune system by presenting the surface antigens of cancer cells as a danger signal to stimulate the immune response further and increase the sensitivity of cancer cells to immune compounds is efficient in removing the tumor by peptides [104].

3.1.2.1. Antilung cancer bioactive peptides. Lung cancer is the deadliest cancer among all types of cancer, with the highest death rate in the world. Smoking, as the main cause of lung cancer, is related to 80–90 % of cases. Since there are more than 20 carcinogens in tobacco smoke, non-smokers are also at risk of lung cancer by inhaling it [105]. As the main organ of respiration, the lungs are responsible for receiving oxygen and leaving carbon dioxide in the inhalation and exhalation processes. Therefore, people with lung cancer are associated with annoying symptoms such as breathing problems, chronic cough, and chest pain. Human lung cancers include two main types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), the latter of which includes 3 subtypes of adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, in order of frequency. In general, NSCLC is the most common type of this malignancy, with 85 % of lung cancer cases [106]. In addition to the development of targeted chemical drugs, many studies have been conducted to identify bioactive peptides for lung cancer treatment in the hope of increasing the survival rate of patients. In a study, wheat germ protein was subjected to hydrolysis with three enzymes, alcalase, pepsin, and proteinase K, and the resulting hydrolysates were evaluated for their antioxidant and anticancer activity on the A549 cell line. Peptides produced by hydrolysis of each enzyme in fractions with more activity have been identified and synthesized. Peptide SSDEEVREEKELDLSSNE is known as the strongest cytotoxic peptide in this study, which was obtained from pepsin enzyme hydrolysates [107]. Magainin 1 and 2 are peptides derived from the skin of *Xenopus laevis*, which, due to their amphiphilic nature and helix structure, their antimicrobial activity has been observed in various studies. Magainin A and G have been synthesized as analogs of these peptides, and their antitumor potential has been investigated for several small cell lung cancer (SCLC) cell lines. Finally, magainin A and G have shown antitumor effects by preventing the growth of cancer cells. Meanwhile, magainin G, with less toxic effects on normal cells, is considered a better option for treatment [108]. In addition, the anticancer activity of a decapeptide called PAP (*Perinereis aibuhitensis* peptide) isolated from a natural marine source (*Perinereis aibuhitensis*) has also been shown on H1299 cells. The treatment of cancer cells with this peptide obtained from enzymatic hydrolysis has led to a decrease in proliferation and cell cycle arrest, as well as an increase in apoptosis due to the enhancement of pro-apoptotic factors compared to anti-apoptotic ones. Therefore, PAP as a suitable candidate has the ability to be used in non-small cell lung cancer treatment [109]. Some of the anti-lung cancer bioactive peptides are listed in Table 1.

3.1.2.2. Antibreast cancer bioactive peptides. Breast cancer is known as the most common malignancy in women around the world, and its development is related to various factors such as heredity, lifestyle, obesity, and aging [110]. Although gender is one of the effective factors in the development of this type of cancer, breast cancer also occurs in men, but it is rare; 100 times more common in women than men [111]. Many oncogenes and anti-oncogenes have been identified whose mutation and unbalanced proliferation play a significant role in causing breast cancer. HER2, EGFR, and BRCA1/2 are among the important genes whose activation and mutation are effective at the beginning of this process [112]. Since breast cancer is a major common problem in the world, access to diagnostic methods and identification of new treatment methods are highly emphasized. In recent years, biological treatments, including the discovery of bioactive peptides from different sources, have been developed to treat this disease. For example, bioactive peptides produced from hydrolysis of casein and whey fractions of goat milk with pepsin and trypsin enzymes have shown anticancer effects against breast cancer cell line (MCF-7). The analyses performed on dead cancer cells treated with peptide fractions have displayed a decrease in the expression of the pyruvate kinase M2, glycogen synthase kinase 3-β, L-lactate dehydrogenase B enzymes, and mucin 1-C and an increase in the expression of receptor-interacting serine/threonine-protein kinase 1 enzyme [113]. Taniya et al. have found that bioactive peptides obtained from the enzymatic digestion of *Amaranthus caudutus* L. (pseudocereal) seed proteins act as an antitumor agent in this type of cancer. The treatment of the MDA-MB-231 cell line with the resulting bioactive peptides has led to the reduction of tumor cell growth and migration, morphological changes in the nucleus and cell membrane, and, as a result, induction of apoptosis [114]. The CPe-III-S peptide (RQSHFANAQP) has been isolated from the hydrolysis product of chickpea albumin, which, in addition to antioxidant activity, has shown anti-proliferative effects against breast cancer cells. The peptide has demonstrated its antitumor activity by binding specifically to p53 and increasing the level of this protein [115]. A list of bioactive peptides derived from different sources against breast cancer is presented in Table 2.

3.1.2.3. Anticolorectal cancer bioactive peptides. Like any other cancer, colorectal cancer is caused by mutations in certain genes. Point mutations are the cause of 70 % of colorectal cancers, which are known as sporadic cancers. Creating a mutation in a specific gene and forming non-malignant adenomas (polyps) can be the basis for the onset of colorectal cancer because about 15 % of these adenomas can turn into carcinomas following other mutations. Of the remaining 30 % of colorectal cancers, 5 % are inherited cancers, and 25 % are familial cancers, which are caused by inherited mutations [84,116]. Various factors play a role in the formation of polyps and the development of colorectal cancer, among which age is considered the most important factor. Hence, the probability of suffering this type of cancer increases significantly in people over 50. Apart from unchangeable factors such as the history of personal or family diseases, lifestyle changes such as a healthy diet, reducing tobacco and alcohol consumption, and increasing physical activities can be effective in reducing the risk of types of cancer, including colorectal [116]. As a new strategy in the treatment, one of the purified

Table 1
Bioactive peptides derived from different sources against lung cancer.

Sources	Bioactive Peptides/Protein Hydrolysates	Target cell line(s)	Peptide concentration in cell assays	References
Blood clam (*Tegillarca granosa*) muscle	WPP (398.44 Da)	H-1299 cell line	Final concentrations of 1.5, 2, 2.5, 3, 4, and 5 mg/mL in MTT assay and IC_{50} value 3.3 mg/mL	[209]
Ruditapes philippinarum	AVLVDKQCPD (1950 Da)	A549 cell line	The final concentration of 0–2.0 mg/mL in MTT assay and LC_{50} value 1.35 mg/mL.	[210]
Spider *Lycosa vittata* venom	LVTX-8 (2847.99 Da) IWLTALKFLGKNLGKHLAKQQLSKL	A549 and H460 cell lines	IC_{50} value 8 μM after 24 h incubation and concentrations of 2.5 and 5 μM of peptide for comparative treatment in two cell lines.	[211]
European honey bee (*Apis mellifera*) venom	Melittin (2840 Da) GIGAVLKVLTTGLPALISWIKRKRQQ	A549 cell line	Concentrations of 0, 0.5, 1, 2, or 4 μg/mL of peptide in cell viability assays.	[212]
Wheat germ	SSDEEVREEKELDLSSNE (2136.9 Da)	A549 cell line	Concentrations of 0.3–16 μM peptide and IC_{50} value 2.34 μM.	[107]
African clawed frog (*Xenopus laevis*) skin	Magainin 1 and 2 analogs (Magainin A and G, 2450 and 2473 Da, respectively)	SCLC cell lines: NCI-H82, NCI-H526, NCI-H678, NCI-H735, NCI-H841, and NCI-H889	Concentration ranges of MAG A: 0.83–66.2 μM (2.5–200 μg/mL); MAG G: 0.82–65.7 μM (2.5–200 μg/mL). The average IC_{50} of MAG A against 6 SCLC cell lines: 8.64 μM (range, 6.23–11.7 μM) and MAG G: 8.82 μM (range, 4.44–12.5 μM).	[108]
Perinereis aibuhitensis	PAP (1081.20 Da) IEPGTVGMMF	H1299 cell line	Final concentrations of 0, 0.23, 0.46, 0.69, and 0.92 mM in antiproliferative assay and IC_{50} values 0.69, 0.38, and 0.27 mM at 24, 48 and 72 h, respectively.	[109]
Caribbean sponge (*Smenospongia aurea*)	Smenamides A and B (isomerichybrid peptide/polyketide compounds)	Calu-1 cell line	72 h of treatment with concentrations of 1, 10, 30, 50, 70, and 100 nM in MTT assay and IC_{50} values 48 nM for A and 49 nM for B.	[213]
Spirulina (Arthrospira) platensis	YGFVMPRSGLWFR (1614.8130 Da)	A549 cell line	Concentrations of 31.25–500 μg/mL of peptide in MTT assay and IC_{50} value 104.05 μg/mL.	[214]
Soybean meal	Peptide fractions with molecular sizes of <5 kDa, 5–10 kDa, and 10–50 kDa	NCL-H1299 cell line	The concentration of 800 μg/mL of peptide fractions in MTS assay.	[66]

Table 2
Bioactive peptides derived from different sources against breast cancer.

Sources	Bioactive Peptides/Protein Hydrolysates	Target cell line(s)	Peptide concentration in cell assays	References
Tuna cooking juice	KPEGMDPPLSEPEDRRDGAAGPK (2449.292 Da) and KLPPLLLAKLLMSGKLLAEPCTGR (2562.405 Da)	MCF-7 cell line	The concentration of 1 mg/mL of hydrolysates and its fractions and 0–5 mg/mL $PAH_{2.5}$ for determining antiproliferative activity with IC_{50} value 1.39 mg/mL.	[215]
Common bean (*Phaseolus vulgaris*) Legumi Secchi cultivar	Hemagglutinin (N-terminal sequence: ANDISFNFVRFNETNLILGG)	MCF-7 cell line	Concentrations of 10–10000 nM of peptide in MTT assay and IC_{50} value 0.2 μM.	[216]
Tuna dark muscle by-product	(1) LPHVLTPEAGAT (1206 Da) and (2) PTAEGGVYMVT (1124 Da)	MCF-7 cell line	1 mg/mL of hydrolysates and various concentrations of fractions in MTT assay with IC_{50} values of 8.1 and 8.8 μM for peptides (1) and (2), recpectively.	[217]
Chickpea	CPe-III (1155 Da) RQSHFANAQP	MCF-7 and MDA-MB-231 cell lines	Concentrations of 0.5, 1, 1.5, 2 and 2.5 μmol/mL in MTT assay and EC50 values of 2.38 μmol/mL for MCF-7 and 1.50 μmol/mL for MDA-MB-231.	[115]
Ruditapes philippinarum	AVLVDKQCPD (1950 Da)	MDA-MB-231 cell line	The final concentration of 0–2.0 mg/mL in MTT assay and LC_{50} value 1.58 mg/mL.	[210]
Dendrobium catenatum Lindley	RHPFDGPLLPPGD (1416.8370 Da), RCGVNAFLPKSYLVHFGWKLLFHFD (2993.7427 Da) and KPEEVGGAGDRWTC (1503.8099 Da)	MCF-7 cell line	The concentration of 500 μg/mL of P1, P2, and P3 in MTT assay.	[218]
Walnut (*Juglans regia* L.)	CTLEW (651.2795 Da)	MCF-7 cell line	Treatment with concentrations of 0.5 and 1 mg/mL of peptide for 48 h in apoptosis and cell cycle distribution analyses.	[45]
Olive seed	LLPSY (591.3268 Da)	MDA-MB-468 cell line	Concentrations of 0, 50, 75, 150, 300 and 500 μg/mL in MTT assay and IC_{50} value 97.6 ± 1.9 μg/mL.	[64]
Xenopus laevis skin secretion	XLAsp-P1 (607.7 Da) DEDDD	MCF-7 cell line	Concentrations from 0 to 50 μg/mL of peptide in MTT assay and LC_{50} value less than 5 μg/mL	[219]
Bovine β-casein	INKKI	MCF-7 cell line	Concentrations from 145 nM to 0.28 nM in MTT assay and $IC_{50\ \%}$ value was 3.78 μg/mL.	[220]
Soybean	Lunasin (43 amino acids, 5.5 kDa)	MDA-MB-231 cell line	Concentration ranges from 0.1 to 200 μM in MTT assay and IC_{50} value 181 μM.	[221]
Chinese lima bean (*Phaseolus lunatus* L.)	Lunatusin (7 kDa)	MCF-7 cell line	Concentrations from 0 to 160 μM in MTT assay and IC_{50} value 5.71 μM.	[51]
Rice bran	EQRPR (685.378 Da)	MCF-7 and MDA-MB-231 cell lines	Dosage of peptide from 100 to 1000 μg/mL in MTS assay.	[48]
Red and brown *Lens culinaris*	Twenty-eight peptides have been sequenced from fractions with MW $\leq$ 3 kDa	MCF-7 cell line	Concentrations of 5, 10, 15, 20, and 30 mg/mL in MTT assay and IC_{50} value 12.27 mg/mL.	[222]

bioactive peptides against this cancer is SCAP1 (with LANAK sequence) from oyster (*Saccostrea cucullata*), which has been identified to have anticarcinogenesis ability against HT-29 human colon carcinoma cell line [117]. *Spirulina* is an edible blue-green alga that contains about 60 % protein, and its potential in the treatment of diseases, including cancer, has been proven [118]. Wang et al. have selected this protein-rich source as a precursor for the production of bioactive peptides and have shown the antiproliferative effect of the resulting peptide fractions on various cancer cell lines. The peptide HVLSRAPR, with a high potential to inhibit the human colorectal adenocarcinoma cell line (HT-29), has been reported by this group [119]. In addition, in another study, five peptides GLTSK, LSGNK, GEGSGA, MPACGSS, and MTEEY have been isolated from the common bean, and their anti-proliferative effect on colorectal cancer cells have been demonstrated by modulating the factors involved in apoptosis and cell cycle [120]. Table 3 shows examples of anti-colorectal cancer bioactive peptides.

3.1.2.4. Antiprostate cancer bioactive peptides. Prostate cancer is known as one of the most commonly diagnosed cancers in men, affecting approximately 1 in 25 men in the world [121]. In fact, the prostate is an important gland in the male urogenital system because it plays a crucial role in semen production and, in this way, helps to protect and transfer the sperm produced in the testicles. The prostate is normally the size of a walnut in healthy people, but it usually enlarges with age, which refers to benign prostatic hyperplasia [122]. In addition to age, race, genetics, family history, smoking, nutrition, and obesity are among the basic risk factors in the development of this cancer [85]. PSA (prostate-specific antigen) level, as one of the enzymes in the prostate fluid, is routinely measured in order to check the health of the prostate. Although performing this test can help early detection of cancer and increase survival, it also comes with disadvantages, such as showing false results [123]. Apart from conventional treatments, many bioactive

Table 3
Bioactive peptides derived from different sources against colorectal cancer.

Sources	Bioactive Peptides/Protein Hydrolysates	Target cell line(s)	Peptide concentration in cell assays	References
Spirulina platensis	HVLSRAPR (935.1 Da)	HT-29 cell line	IC_{50} value of 99.88 **μ**g mL^{-1}.	[119]
Walnut (*Juglans regia* L.)	CTLEW (651.2795 Da)	Caco-2 cell line	Treatment with concentrations of 0.5,1,2,3,4 mg/mL for 48 h in MTT assay and IC_{50} value 0.65 ± 0.42 mg/mL.	[45]
Oyster (*Saccostrea cucullata*)	LANAK (515.29 Da)	HT-29 cell line	Concentrations from 10 to 100 μg in MTT assay and IC_{50} values of 90.31 ± 0.45, 70.87 ± 0.82, and 60.21 ± 0.45 μg/mL for 24, 48 and 72 h of incubation respectively.	[117]
Quinoa (*Chenopodium quinoa* Willd.)	LWREGM (790.32 Da), DKDYPK (764.40 Da), IFQEYI (811.30 Da), DVYSPEAG (836.44 Da), and RELGEWGI (958.50 Da)	Caco-2, HT-29, and HCT-116 cell lines	IC_{50} value of 0.600 ± 0.006, 0.594 ± 0.003 and 0.195 ± 0.001 mg peptide/mL of F-1, F-2 and F-3 fractions for HT-29, respectively. 0.746 ± 0.001, 0.807 ± 0.008 and 0.193 ± 0.003 mg peptide/mL of F-1, F-2 and F-3 for HCT-116, respectively. 0.256 ± 0.004 mg peptide/mL of F-3 for Caco-2.	[223]
Common bean (*Phaseolus vulgaris* L.)	GLTSK (505.48 Da), LSGNK (518.29 Da), GEGSGA (521.22 Da), MPACGSS (656.01 Da) and MTEEY (671.98 Da)	HCT-116, RKO, and KM12-L4 cell lines	Concentrations of peptide extracts from 0.125 to 1 mg/mL in MTS assay and AH-PE-IC_{50} = 0.53 mg/mL for HCT-116 and BM-PE-IC_{50} = 0.51 mg/mL for RKO.	[120]
Soybean meal	Peptide fractions with molecular sizes of <5 kDa, 5–10 kDa, and 10–50 kDa	HCT-116 and Caco-2 cell lines	The concentration of 800 μg/mL of peptide fractions in MTS assay.	[66]
Soybean	Lunasin (43 amino acids, 5.5 kDa)	HCT-116, KM12-L4, RKO, and HT-29 cell lines	Concentrations of 0–100 μM in MTS assay and IC_{50} values 13 μM for KM12-L4, 21.6 μM for RKO, 26.3 μM for HCT-116 and 61.7 μM for HT-29.	[224]
Bitter gourd (*Momordica Charantia* L.) seeds	BG-4 (4 kDa)	HCT-116 and HT-29 cell lines	Concentrations of 0–1000 μg/mL in MTS assay and ED_{50} values of 134.4 and 217.0 μg/mL for HCT-116 and HT-29, respectively.	[46]
Rice bran	EQRPR (685.378 Da)	Caco-2 and HCT-116 cell lines	Dosage of peptide from 100 to 1000 μg/mL in MTS assay.	[48]
Solitary tunicate (*Styela clava*)	Peptide fraction with MW 3.6 ± 0.1 kDa	DLD-1 cell line	Concentrations of 100–1000 μg/mL in MTT assay and IC_{50} value of 1163.3 μg/mL.	[225]

Table 4
Bioactive peptides derived from different sources against prostate cancer.

Sources	Bioactive Peptides/Protein Hydrolysates	Target cell line (s)	Peptide concentration in cell assays	References
Sepia ink	QPK (343.4 Da)	DU-145, PC-3, and LNCaP cell lines	Treatment with concentrations of 3, 5, 7, 10, 13 and 15 mg/mL of peptide for 24, 48, and 72 h in CCK-8 assay.	[125]
Ruditapes philippinarum	AVLVDKQCPD (1950 Da)	PC-3 cell line	The final concentration of 0–2.0 mg/mL in MTT assay and LC_{50} value 1.29 mg/mL.	[210]
Setipinna taty	YALPAH (670.77 Da)	PC-3 cell line	Concentration ranges from 1 to 9 mg/mL in MTT assay and IC_{50} value 11.3 mg/mL or 16.9 μM.	[226]
Olive seed	LLPSY (591.3268 Da)	PC-3 cell line	Concentrations of 0, 50, 75, 150, 300 and 500 μg/mL in MTT assay and IC_{50} value 86.1 ± 2.6 μg/mL.	[64]
Blood clam (*Tegillarca granosa*) muscle	WPP (398.44 Da)	PC-3 and DU-145 cell lines	Final concentrations of 1.5, 2, 2.5, 3, 4, and 5 mg/mL in MTT assay and IC_{50} values 1.99 and 2.80 mg/mL in inhibition of two cell lines.	[209]
Anthopleura anjunae	(AAP-H, YVPGP) (531.60 Da)	DU-145 cell line	Final concentrations of 1.883, 5.650, 9.416, 13.183, 16.949, or 20.716 mM in MTT assay and IC_{50} values 9.605, 7.910, and 2.298 mM at 24, 48, and 72 h, respectively.	[227]
South American tree frog (*Phyllomedusa bicolor*) skin secretions	Dermaseptins B2 (33 residues, 3180 Da) and B3 (28 residues, 2780 Da)	PC-3 cell line	Concentrations of 0, 0.25, 0.5, 1, 2.5, 5 and 7.5 μM and EC_{50} values about 2 μM for Drs B2 and 3 μM for Drs B3.	[33]
Spider toxin	Lycosin-I	DU-145 and PC-3 cell lines	Concentrations of 5, 10, and 20 μmol/L of peptide in MTT assay.	[228]
Honey bee venom	Melittin (2840 Da)	LNCaP, DU-145, and PC-3 cell lines	Concentrations of 0.5, 1, and 2.5 μg/mL of peptide for 24, 48, and 72 h in cell viability assay.	[127]
Red and brown *Lens culinaris*	Twenty-eight peptides have been sequenced from fractions with MW ≤ 3 kDa	PC3 cell line	Concentrations of 0.5, 2.5, 5, and 7.5 mg/mL in MTT assay and IC_{50} value 0.96 mg/mL.	[222]

peptides have been identified for the treatment of prostate cancer. TFD_{100} is a glycopeptide derived from Pacific cod that prevents the binding of β-galactoside–binding lectin (galectin-3) to the Thomsen-Friedenreich disaccharide (TFD) of the cancer cell surface. Since the interaction of gal3–TFD is involved in angiogenesis, metastasis, immunity attenuation, and overall tumor progression, blocking it has led to a decrease in prostate cancer development [124]. A tripeptide (QPK) purified from *Sepia ink* has inhibited the proliferation of three prostate cancer cell lines. This peptide, by increasing the expression of pro-apoptotic protein Bax and decreasing the anti-apoptotic protein Bcl-2 and simultaneous upregulation of caspase 3, has led to the induction of apoptosis as well as cell cycle arrest [125]. Melittin is a peptide with 26 amino acid residues found in bee venom, which, by accumulating in the plasma membrane or the membrane of organelles such as mitochondria, causes cell lysis and death [126]. In a study, Park et al. evaluated the ability of melittin to suppress the growth and proliferation of prostate cancer cells. The results obtained from *in vitro* and *in vivo* assays have shown that this peptide, by inactivating NF-kB as an important factor in reducing the death of cancer cells, has led to the induction of apoptosis and reduced tumor progression [127]. In addition, the antitumor effects of melittin in various other cancers have also been confirmed in several studies [128–130]. More examples of bioactive peptides identified against prostate cancer are shown in Table 4.

3.1.2.5. Antimelanoma bioactive peptides. Melanoma and non-melanoma are the main forms of skin cancer. Melanoma, despite being less common, is known as the most aggressive and deadly type of skin tumor [86]. This type of skin cancer is formed in the deepest cells of the epidermis layer called melanocytes, which are responsible for the production of skin pigments or melanin. The ability to invade nearby tissues and rapid metastasis is one of the threatening characteristics of melanoma, which reduces the survival rate in patients [131]. In addition to the conventional treatments of chemotherapy, radiation therapy, immunotherapy, and surgery, bioactive peptides have also been studied for the treatment of melanoma, and favorable results have been obtained from them, which can help improve the treatment of patients [132]. An example of these studies is the identification of the peptide INKKI as an anticancer agent and suitable drug candidate for the treatment of melanoma. This peptide isolated from bovine β-casein has been used to evaluate the anti-proliferative and antitumor effects *in vitro* and *in vivo*. In this study, INKKI has led to toxicity in B16F10 melanoma cells and increased apoptosis, as well as decreased tumor volume and metastasis in mice treated with the peptide [133]. Pentadactylin is an antimicrobial peptide derived from the skin secretions of the *Leptodactylus labyrinthicus*. Examining the effect of this peptide on the melanoma cell line (B16F10) has shown its ability to cause toxicity and induce apoptosis in these cancer cells [134]. Moreover, the effect of Lunasin isolated from soybeans has also been evaluated on human melanoma cells, and it is known as an anticancer agent that targets this type of cancer [135]. Table 5 lists some of the bioactive peptides from different sources against melanoma.

3.1.3. Action mechanisms of bioactive peptides in cancer

3.1.3.1. Mechanisms related to plasma membrane disruption. Since the plasma membrane is an essential protective barrier for cell survival, its disruption leads to the induction of cell death and is one of the mechanisms of peptide-based drugs or anticancer peptides. The difference in the membrane of cancer and normal cells, including the presence of a large negative charge resulting from the exposure of anionic molecules such as phosphatidylserine (PS) on the surface of cancer cells compared to the neutral charge of the

Table 5
Bioactive peptides derived from different sources against melanoma.

Sources	Bioactive Peptides/Protein Hydrolysates	Target cell line (s)	Peptide concentration in cell assays	References
Bovine β-casein	INKKI	B16F10 cell line	Concentrations of 20 μM–0.03 μM of peptide in MTT assay and IC_{50} 1.7 μM.	[133]
Bovine lactoferricin	LTX-315 (Nonamer)	A375 cell line	Concentration ranges from 2 to 180 μm/mL in MTT assay and IC_{50} value 30 μM after 5 min.	[152]
Myxoma virus	Myxoma virus protein analogue (RRM-MV, 18 aa; MW 2.34 kDa)	MM96L cell line	Treatment with concentrations of 100–1600 ng/mL for 3 h or 25–800 ng/mL for 18 h in MTT assay.	[229]
Frog *Leptodactylus labyrinthicus* skin secretions	Pentadactylin (2541.29 Da)	B16F10 cell line	Concentration ranges from 0 to 128 μM in MTT assay and IC_{50} value 25.7 μM and IC_{75} value 30 μM.	[134]
Soybean	Lunasin (43 amino acids, 5.5 kDa)	SKMEL-28 and A375 cell lines	Concentration range of 10–100 μM in MTS assay.	[135]
South American rattlesnake venom (*Crotalus durissus terrificus*)	Crotamine (4800 Da)	B16F10 and SK-Mel-28 cell lines	Concentration of 1 and 5 μg/mL in MTT assay.	[230]
Snake *Bungarus fasciatus* venom	Cathelicidin-BF (BF-30, 3637.54 Da)	B16F10 cell line	Concentrations from 0 to 80 μM in MTT assay and IC_{50} of 7.3 μM.	[231]
Derivative of human lactoferricin	R-DIM-P-LF11-322 (2677.4 Da)	A375 cell line	IC_{50} of 9.5 ± 0.3 μM.	[232]
Dwarf honey bee *(Apis florea)* venom	Melittin (~3 kDa) GIGAILKVLATGLPTLISWIKNKRKQG	A375 cell line	Concentrations of 0–5 μg/mL in MTT assay and IC_{50} value of 3.38 ± 0.16 μg/mL.	[233]
Spider *Lycosa vittata* venom	LVTX-9-C_{18} (2117.76 Da)	B16F10 cell line	IC_{50} value 8.5 ± 2.9 μM in serum-containing medium and 4.4 ± 0.2 μM in serum-free medium.	[234]

membrane of non-cancerous cells, is a key factor for targeting by cationic peptides [136,137]. By adsorbing cationic peptides and binding to anionic compounds, the integrity and stability of the cell membrane are disrupted, followed by cell death. In contrast, the high cholesterol content of the membrane of normal cells is the limiting factor for their entry into the cell. In fact, the establishment of electrostatic peptide-lipid interaction is considered the initial and important step for membrane depolarization and, ultimately, cell death [138].

Membrane disruption by anticancer bioactive peptides usually occurs through three distinct modes, including barrel-stave, toroidal pore, and carpet models (Fig. 3) [139]. In the barrel-stave model, first, the peptides are attached to the membrane surface in a parallel and helical form. Then, these helical peptides penetrate vertically into the bilayer membrane and form a barrel-stave like channel with a diameter of 2–9 nm so that the polar groups of the peptides are placed towards the lumen of the pore and the non-polar groups are placed towards the lipid bilayers of the membrane. Indeed, in this model, helical peptides are used as the building staves of the barrel, and as a result, the transmembrane pore is created [140,141]. In the toroidal pore model, the insertion of peptides into the membrane leads to the bending of the lipids and the formation of a toroidal-shaped hole from the peptide and lipid mixture. In other words, peptides force the lipid monolayer to bend from top to bottom with the pressure they create so that a toroidal pore is formed from the connection of peptides and phospholipid head groups [142]. In the carpet model, peptides are extensively bound to the membrane by electrostatic interactions. This connection is such that the peptides spread parallel to the membrane plane, from the side of their hydrophobic groups, on the surface of the bilayer membrane, similar to a carpet. With the increase in the number of surface peptides and reaching a threshold in a surfactant-like action, the membrane is disintegrated, and micellization occurs [139,140].

In general, peptides use any of the mechanisms to exert their anticancer effects based on their characteristics and the properties of the desired membrane. Many antimicrobial peptides have been reported to destroy cancer cells by cell membrane lysis. For example, the peptide pardaxin derived from fish has shown that in the presence of phosphatidylcholine and phosphatidylglycerol of the membrane, it uses barrel-stave and carpet mechanisms, respectively, so it has been effective in killing HT-1080 human fibrosarcoma cells by disrupting the membrane [143,144]. Moreover, other antimicrobial and cationic peptides, such as Gomesin (QCRRLCYKQRCVTYCRGR) isolated from Brazilian tarantula *Acanthoscurria gomesiana* haemocytes and human cathelicidin LL-37 (LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLVPRTES), respectively, use the carpet and toroidal pore modes of action to destroy the membrane and kill cancer cells [145,146].

3.1.3.2. Mechanisms related to mitochondria. In the previous models, cell death occurred due to disruption of the cell membrane, but anticancer peptides can target the intrinsic pathway without disrupting the plasma membrane and induce cell death by destroying the mitochondrial membrane [147]. Therefore, familiarity with this pathway can help us better understand the function of bioactive peptides. Stimuli such as oncogenes, hypoxia, and damage to DNA induce the beginning of apoptosis through this pathway so that by

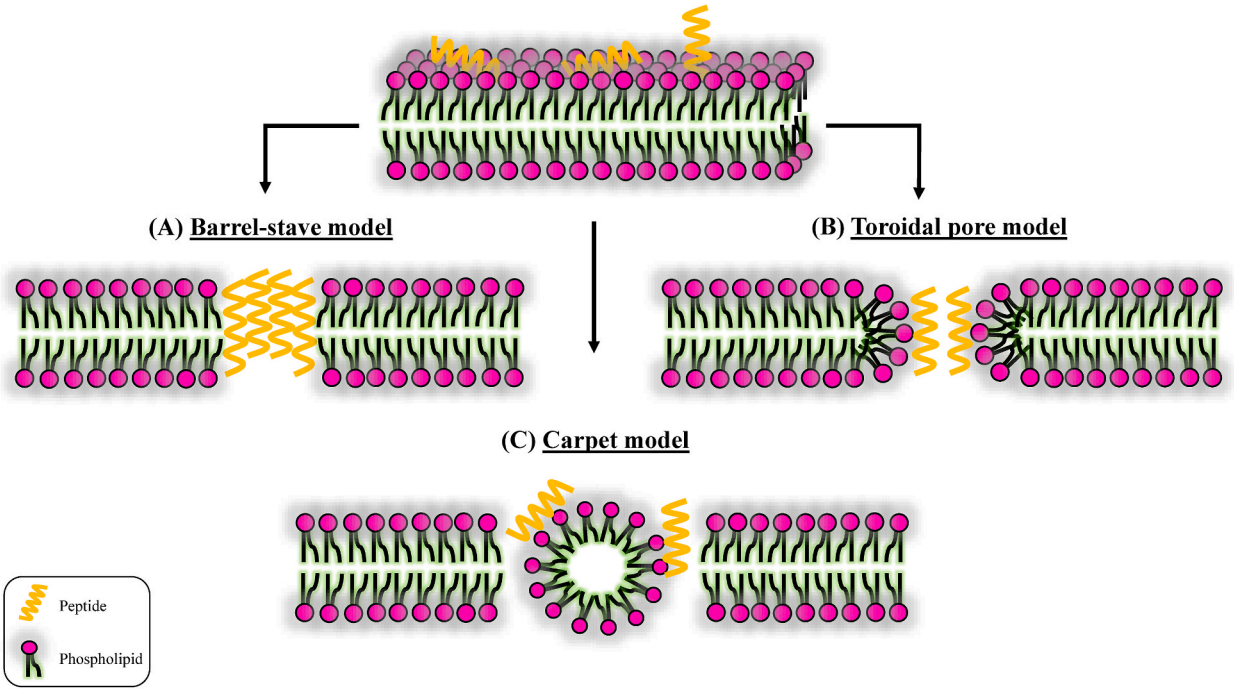

Fig. 3. Schematic illustration of three recognized action mechanisms of anticancer peptides related to plasma membrane disruption. (A) Barrel-stave model: Peptides insert into the bilayer membrane in a perpendicular orientation and form transmembrane pores. (B) Tororial pore model: Penetration of peptides leads to bending of membrane lipids and formation of mixed pores of peptide and lipid. (C) Carpet model: The surface of the membrane is covered by a wide layer of peptides. Eventually, after membrane permeation and disintegration, micelles are formed.

creating pores in the outer membrane of mitochondria, factors such as cytochrome *c* are released from mitochondria into the cytosol [148]. Proteins of Bcl-2 family members, which include two types of apoptosis inhibitors or anti-apoptotic, such as Bcl-2 and Bcl-X, and apoptosis inducers or pro-apoptotic, such as Bax and Bak, are responsible for regulating this pathway. The release of cytochrome *c* and its assembly in the cytosol together with apoptotic proteinase activating factor1 (Apaf-1), ATP, and pro-caspase 9 to form the proteasome complex leads to the activation of a cascade of downstream caspases. Caspases, as a group of aspartate-specific cysteine proteases, play a significant role in both intrinsic and extrinsic pathways of apoptosis. Caspase 9 is the initiator caspase of the mitochondrial pathway that finally activates the executive caspase 3 to cause cell death through proteolysis of multiple cellular structures [149,150]. Valero et al. showed that Bax-derived poropeptide, which contains membrane-interacting and pore-forming regions, is able to act directly and independently of endogenous proteins to induce apoptosis by creating permeability in the mitochondrial outer membrane [151]. In a study, the oncolytic activity of peptide LTX-315 derived from bovine lactoferricin on A375 human melanoma cells has been reported. This peptide has exerted its anticancer effects by disrupting both the plasma membrane and the mitochondria. Overall, the treatment of target cells with LTX-315 has shown the depolarization of the mitochondrial membrane, morphological changes in it, and the release of death associate molecular patterns, including cytochrome *c*, ATP, and HMGB1 from the damaged mitochondria and nucleus [152]. Another example of peptides that trigger apoptosis of cancer cells through mechanisms related to mitochondria can be referred to KLA peptide, (KLAKLAKKLAKLAK), which is a known antimicrobial cationic peptide [153]. The synergistic effect of KLA peptide and radiation as a combinational therapy has been indicated to increase the apoptosis of leukemia cell line [154].

3.1.3.3. Mechanisms related to p53 activity. p53, which is known as a tumor suppressor protein, is encoded by the *TP53* gene. Under normal conditions, any stress and damage to the cell leads to the activation of p53 so that this protein, with its important role in various cellular processes, can repair genome damage, stop the cell cycle, and induce cell death [155]. Structurally, p53 is a tetrameric protein that contains four polypeptide chains, including N-terminal domain (NTD), DNA-binding domain (DBD), oligomerization domain (OD), and C-terminal domain (CTD) as regulator [156]. P53, as a key transcription factor, initiates pathways related to apoptosis so that by increasing the permeability of the mitochondrial outer membrane and releasing proteins such as cytochrome *c*, it activates caspase cascades, thus preventing tumor progression. However, in more than 50 % of different cancers, the mutation in p53 has been clearly observed, so in this situation, due to the lack of cell cycle arrest, the DNA defect is transmitted to the next generation through replication. Since the half-life of this protein is short, in healthy cells, it is degraded by proteasome after about 20 min [157]. One of the strategies of bioactive peptides to inhibit cancer is to prevent the proteolysis of p53 and increase its expression level in the cell. For example, peptide p28, derived from azurin by inhibiting the interaction between p53 and E3 ubiquitin-protein ligase, has led to an increase in its post-translational level in breast cancer and melanoma cells. The results of molecular dynamics simulation in this study showed that this peptide blocked the interaction of P53 with COP1 (constitutively photomorphogenic 1) via binding to the DNA-binding domain (DBD) [158]. Due to COP1 overexpression in various malignancies, silencing its function has been demonstrated to increase p53 levels, arrest the cell cycle, and thus reduce tumor growth [159]. Recently, He et al. have reported that the peptide fractions obtained from Sacha inchi (*Plukenetia volubilis*) have anti-hepatoma effects. The peptides identified in this research, including LLEPDVR, ALVEKAKAS, and TGDGSLRPY, have shown the best performance in inhibiting the proliferation of HepG2 cells by increasing the level of P53 and the pathway related to mitochondria and have been introduced as new agents in the treatment of liver cancer [160].

3.1.3.4. Mechanisms related to ion channels. Ion channels are a group of proteins in cell membranes and different organelles that selectively allow the entry and exit of certain ions. Various stimuli are able to open the aqueous pore in ion channels, based on which these channels are classified into two types: voltage-gated channels and ligand-gated channels [161]. These transmembrane proteins are effective in maintaining the homeostasis of the cell by the specialized passage of ions from one side of the membrane to the other, and by transmitting signals inside the cell, they are implicated in various physiological processes, including growth, proliferation, migration and cell death [162]. In cancer cells, there is abnormal expression or dysregulated function of ion channels, especially sodium, potassium, chloride, and calcium channels, which are involved in the hallmarks of cancer, such as continuous and uncontrolled proliferation, metastasis, and tumor invasion [163]. Therefore, blocking ion channels by therapeutic agents can have a significant effect on preventing the development of cancer. Bioactive peptides are one of these agents that provide an avenue to confront cancer and have shown promising results to date. For example, a peptide called chlorotoxin is derived from scorpion venom, whose inhibitory effect on CLC-3 has been observed as a member of the voltage-gated Cl^- channel family [164]. Since changes in cell volume are required for the proliferation process and ion channels such as chloride are responsible for regulating it, the inhibition of CLC-3 channel function by peptide has led to the reduction of migration and invasion of glioma tumors [165]. In another study, Bowen et al. obtained two peptides, SOR-C13 (KEFLHPSKVDLPR) and SOR-C27 (EGKLSSNDTEGGLCKEFLHPSKVDLPR), from the carboxyl terminus of the longer peptide soricidin derived from the northern short-tailed shrew venom. *In vivo* experiments have shown that these peptides have positive effects in mice with prostate or ovarian tumors by blocking calcium channels of transient receptor potential vanilloid 6 (TRPV6), which are highly expressed in a range of carcinomas [166].

4. Production methods of bioactive peptides

There are different methods to obtain biologically active peptides, including enzymatic hydrolysis, microbial fermentation, chemical synthesis, and recombinant DNA technology. Although each of these methods has its own advantages and disadvantages, the

first two are the most common methods used to access bioactive peptides (Fig. 4).

4.1. Enzymatic hydrolysis

Enzymatic hydrolysis can be performed by various enzymes, either individually or in combination. The simplest method is to use digestive enzymes such as pepsin, trypsin, and chymotrypsin. An advantage of using digestive enzymes is the possibility of oral administration of bioactive peptides due to simulating the human gastrointestinal tract [167]. For example, Capriotti et al. identified many bioactive peptides from soybean seeds and soy milk by gastrointestinal digestion simulation *in vitro* [168]. In addition, enzymatic hydrolysis can be carried out by proteolytic enzymes derived from plants, animals, and microorganisms at optimal temperature and pH. In a study, Chinese quince (*Cydonia oblonga*) seed protein has been hydrolyzed by papain enzyme, and finally, the potential of two peptides identified with the sequence of NYRRE and RHAKF has been evaluated in the field of skincare. The results have shown the better performance of RHAKF in antioxidant assays, tyrosinase inhibition, and copper chelation [169]. In general, the enzymatic hydrolysis method is desirable and used by researchers due to its repeatability, easy control of the hydrolysis process, short time, and low cost. The type of enzyme used, the ratio of enzyme to substrate, and the time of hydrolysis are among the important factors that affect the kind of final product [170]. The produced hydrolysates are then centrifuged to separate the bioactive peptides present in the supernatant from the undigested proteins in the precipitate. In the following steps, the processes of purification and structural characterization are carried out using different techniques.

4.2. Microbial fermentation

Another common method used to produce bioactive peptides is microbial fermentation, in which protein substrates are subjected to hydrolysis by the proteolytic system of microorganisms such as bacteria, yeast, and mold. The combined use of these microorganisms in the fermentation process can enhance proteolysis [171]. *Lactobacillales* or lactic acid bacteria (LAB) are probiotics that play an important role in the production of bioactive peptides, especially from food proteins. The proteolytic system in these bacteria consists of a complex of proteins attached to the cell wall, transporters, and intracellular peptidases, which are respectively involved in the initial breakdown of high molecular weight proteins into oligopeptides, their transfer to the cytoplasm and the completion of the hydrolysis process and ultimately the production of peptides with low molecular weight and free amino acids [172]. In general, the type of strain selected in fermentation is considered a key point because the difference in the proteolytic system of microorganisms

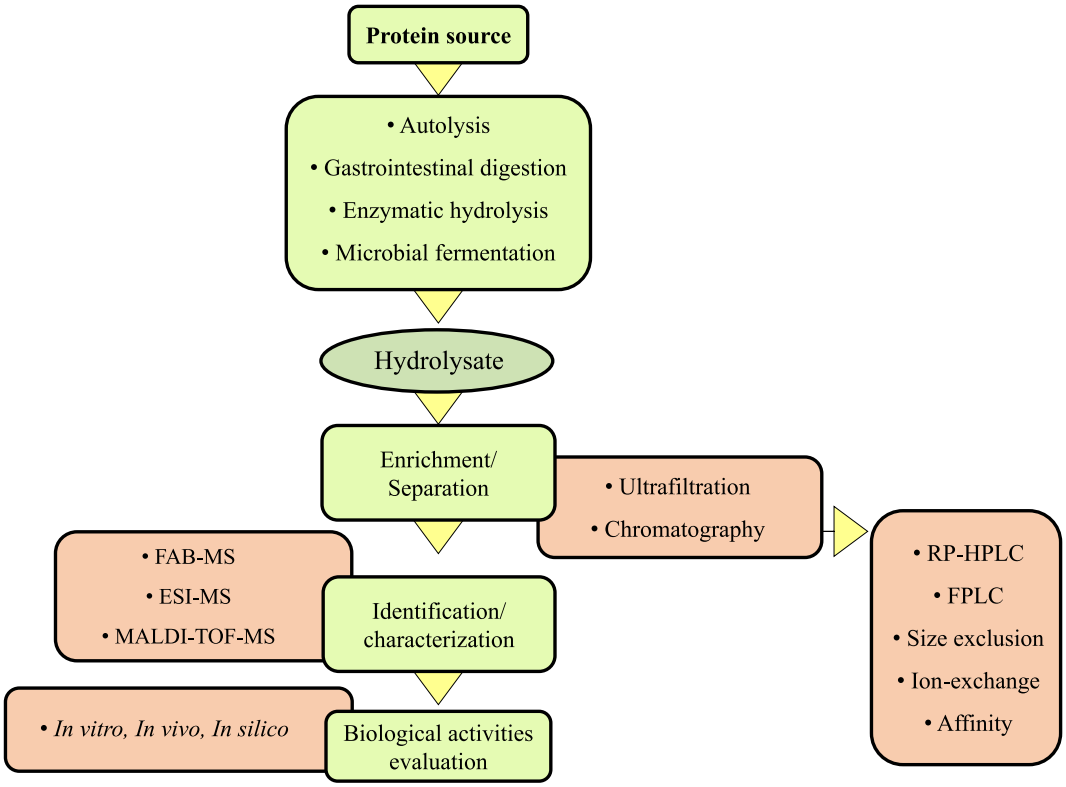

Fig. 4. Schematic diagram of the isolation, purification, and identification of bioactive peptides from protein sources. RP-HPLC: reversed-phase high-performance liquid chromatography, FPLC: fast protein liquid chromatography, FAB-MS: fast atom bombardment mass spectrometry, ESI-MS: electrospray ionization mass spectrometry, MALDI-TOF-MS: matrix-assisted laser desorption/ionization time-of-flight mass spectrometry.

leads to the production of peptides with different biological functions [173]. The production of bioactive peptides from milk and other dairy products by fermentation is one of the common strategies. Kefir is fermented milk whose cauliflower-like grains are formed from the symbiosis of yeasts and lactic acid bacteria and is prepared by adding these grains to raw milk. The therapeutic potential of kefir, including its anticancer effect, has been confirmed in various cancers such as breast, leukemia, gastric, skin, and colon [174]. In another study, using the combined methods of enzymatic hydrolysis and fermentation, Wang et al. identified an anticancer tripeptide with the sequence Trp-Thr-Pro from rapeseed (*Brassica campestris* L.), which by increasing the expression of p53 and Bax proteins and decreasing the expression of Bcl-2, has led to the induction of apoptosis and inhibition of the proliferation of human liver cancer cell line (HepG2) [175].

4.3. Chemical synthesis

Chemical synthesis is another widely used method for producing bioactive peptides, carried out in two major protocols: solid-phase peptide synthesis (SPPS) and solution-phase synthesis (SPS). Solution phase synthesis is an old method that was first invented in 1953, ten years before the solid phase, to produce insulin peptides [176]. The basis of the SPS method is the pairing of individual amino acids in a solution medium; further, combinatorial condensation is used to synthesize long peptide chains. One of the most important advantages of this method is the low cost of materials and equipment. Also, it is possible to purify the produced products at each stage of the synthesis and obtain a large number of high-quality peptides. However, the long reaction time and production of intermediates and chemical waste are important limitations of this method [177]. Solid-phase synthesis was first reported in 1963 by Robert Bruce Merrifield [178]. The technique used in this method is that initially, the side chains groups and N-terminal of the first amino acid are covered by protective groups in order to prevent the occurrence of additional reactions and deviation from the main path. Then, the amino acid is attached from the C-terminal to the resin substrate, which acts as an anchor, and immediately after the connection, the step of deprotection from the amine end and washing of unwanted materials is done so that by adding the second amino acid, the conditions for the coupling of the two amino acids with each other are provided. After the amino acids are joined together, another wash is performed to introduce the resin-peptide into the next cycle. This cycle is repeated until, finally, the peptide with the desired sequence is produced and separated from the resin [179,180]. 9-fluorenylmethyloxycarbonyl (FMOC) and t-butyloxycarbonyl (BOC) are two of the main amino protective groups. Nowadays, the use of FMOC in solid-phase synthesis has become one of the most widely used strategies for the chemical production of many drugs and peptides due to its easy removal by piperidine and more efficient peptides [181]. Compared to the solution phase synthesis, the SPPS method is simpler and faster, but the cost of equipment, resin, and reagents is higher.

4.4. Recombinant productions

Recombinant DNA technology, which is also known as genetic engineering and gene-splicing technology, is a cost-effective method that is capable of mass and large-scale production of peptides, especially with long chains. In this method, modern techniques of cloning and gene expression are used to produce one or more recombinant peptides. The main process is that a foreign gene (the gene encoding the desired peptide) is inserted into a vector to be copied, transcribed, and translated in a suitable expression system [182]. The expression systems of bioactive peptides include prokaryotic and eukaryotic expression systems, which, due to the advantages of using prokaryotic cells, is one of the most common systems for producing recombinant proteins/peptides, *Escherichia coli* bacteria (*E. coli*). *E. coli* expression system is generally enhanced with fusion proteins and tandem genes to raise the expression level of bioactive peptides [183]. Antimicrobial peptides produced by this method are usually expressed as fusion proteins due to their sensitivity to proteases. Anticancer fusion peptide (ACFP) derived from milk proteins has been prepared through genetic engineering so that it has been expressed using recombinant plasmid pGEX-KG-ACFP in *E. coli*, and after purification, its anticancer effect has been observed on SKOV3 human ovarian cancer cell line [184]. Despite the existing limitations and costs, many pharmaceutical peptides are produced through the last two methods individually or in combination [10].

After the proteolysis process, the supernatant containing low molecular weight peptides is recovered, and various chromatography and ultrafiltration techniques are used for fractionation and purification. Finally, the amino acid sequence can be identified by mass spectrometry to investigate the biological functions of the resulting peptides [185].

5. Safety of bioactive peptides

When bioactive compounds such as proteins and peptides are introduced as functional foods and nutraceuticals to exert beneficial effects on health, validation of the health claims attributed to them is considered an essential prerequisite. This means that the adverse consequences that a compound may have when consumed are investigated and eliminated before adding to food or medicine, so a comprehensive safety evaluation of the product is needed to avoid possible risks to human health before being made available to the public [186]. Disturbance in the intestinal wall, toxicity of erythrocytes and lymphocytes, production of free radicals, enzymopathic and immunopathic tissue damage, and cytotoxicity are among the main disadvantages of using peptides in the biological system [187]. For example, celiac disease, which is a genetic autoimmune disorder, is caused by the toxicity of peptides. The consumption of gluten protein (found in foods such as wheat, barley, and rye), followed by disruption of the intestinal walls, is the main cause of this disease [188]. Non-toxic adverse reactions such as allergies are another category of adverse reactions to foods that are mediated immunologically. All compounds that cause allergenicity of foods are protein in nature. Peptide fragments as their breakdown products may retain the allergenic moiety and still act as an allergen. Moreover, the effective dose for the administration of bioactive peptides is

considered an important factor in order to achieve efficacy without adverse effects. Otherwise, their intake in higher doses and long-term can lead to undesirable consequences for the consumer. In general, it is necessary to ensure the level of toxicity and immunogenicity of a peptide in the early stages prior to the formulation of functional foods and therapeutic purposes [189]. Since it is a costly process, the use of computational approaches is an efficient solution. The *in silico* techniques can also be used to evaluate the different physicochemical properties of peptides. Integration of new emerging techniques including metabolomics, proteomics, and peptidomics with conventional methods can contribute to identifying biologically active peptides. Bioinformatics, chemometrics tools, and proteomic/peptidomic methods are the approaches applied in many studies of bioactive peptides. These tools provide the characterization of proteins/peptides and assess their functional, nutritional, and biological relevance, conformation, composition, and interactions to optimize their production and find desired bioactive peptides [190,191].

6. Bioaccessibility and bioavailability of bioactive peptides

Despite the many well-known benefits of bioactive peptides in health, their use in functional foods and nutraceutical supplements is challenging. Although these peptides exert bioactive functions *in vitro*, the situation may differ *in vivo*. Various factors affect the physiological efficiency of bioactive peptides, the most important of which is bioavailability. Initially, bioactive peptides must be released in the gastrointestinal (GI) tract from the food matrix or other vehicles and become accessible in an intact form for absorption, so the process of bioaccessibility is prior to bioavailability. However, bioavailability refers to the amount of absorbed peptides in the target tissues after distribution to apply bioactive effects. The main site of the GI tract for peptide absorption is the small intestine [192,193]. Since the structural characteristics of bioactive peptides are effective in presenting their physiological activities, it is critical that the peptides reach the target site while their structure remains intact [72]. Digestion by peptidases and proteases of the GI tract and possible interaction with its compounds, such as mucin, as well as interaction with food matrix compounds, are important factors affecting the bioaccessibility and bioavailability of bioactive peptides. The most important challenge in this field is that many bioactive peptides are not able to withstand undesirable conditions when passing through the GI tract, so they are subjected to degradation by proteolytic enzymes and lose their structure and, finally, their function. Digestive proteases and peptidases in the GI tract include pepsin, trypsin and chymotrypsin, pancreatic elastase, carboxypeptidases, aminopeptidase, dipeptidases which are located in the stomach, intestinal lumen and brush border, and have a wide range of cleavage sites [193,194]. It has been observed that the presence of proline and its derivatives, such as hydroxyproline, in the peptide sequence could result in their resistance to proteases [195]. For example, the presence of four proline residues in the peptide GPAGPPGPIGNV obtained from Yak (*Bos grunniens*) bones collagen probably plays an important role in enhancing its biostability [196]. In addition to sequence, smaller peptides are more resistant to proteolytic enzymes due to less recognition and cleavage sites. Generally, peptides with lower molecular weight are more accessible to their molecular targets. However, in some cases, enzymatic degradation can be beneficial by releasing latent peptides and exhibiting new bioactivity or even be ineffective [197]. In addition, structural and functional changes that occur due to undesirable reactions between peptides and food matrix compounds during food processing could affect the digestibility, bioaccessibility, and bioavailability of bioactive peptides. Besides the nutritional compositions of the food matrix, various physical forms of consumed food, such as liquid, gel, solid, etc., are also influential in this issue. Therefore, minimizing adverse peptide-food matrix reactions and increasing favorable reactions is one of the required approaches to achieve high bioavailability and bioactivity. Using a suitable food vehicle with less chemical reactivity is a potential strategy for this goal [198,199]. On the other hand, the interaction between bioactive peptides and intestinal mucin can have a negative impact on their passage across mucin and cause a decrease in bioaccessibility. The positive charge and the length of the peptide chain are two leading factors in the interaction with the mucin because the electrostatic interaction between the cationic peptides with the negative charge of mucin, the steric hindrance created by the mucin network for long peptides and various other interactions lead to a decrease in the penetration and absorption of bioactive peptides [200].

Investigation of the transfer mechanisms of bioactive peptides has been done by researchers in order to identify solutions to improve bioavailability. Accordingly, bioactive peptides use four routes, including PepT1 carrier-mediated permeation, passive paracellular transport, transcytosis, and passive transcellular diffusion, to transfer from the intestinal lumen and pass across the epithelium cell to the blood circulation. PepT1, which is mainly located in the intestinal brush-border membrane, belongs to the H + -dependent carrier family. This carrier, which has a high capacity and low affinity, by using the proton electrochemical gradient between the intestinal lumen and epithelial cells and maintaining this gradient through the H+/Na + exchanger, leads to the transfer of some bioactive peptides to the enterocytes. Short chain length (dipeptides and tripeptides), neutral charge, and hydrophobicity of bioactive peptides are important features for binding and PepT1-mediated active transport [201]. PepT2, as another peptide transporter, plays a major role in transporting bioactive peptides to various organs, including the kidney, liver, lung, heart, mammary gland, and brain [202]. In the paracellular pathway, the presence of intestinal tight junctions forms a barrier with selective permeation that allows energy-independent passive diffusion of oligopeptides. Usually, this pathway tends to transfer peptides with low molecular weight, hydrophilic and negatively charged [203]. On the other hand, transcytosis is an energy-dependent transcellular transport route that enables the transfer of long-chain ($\geq$ four residues) and hydrophobic bioactive peptides. In fact, the hydrophobicity of peptides helps their uptake during this process because they are internalized into cells after the establishment of hydrophobic interaction with the apical lipid membrane of intestinal epithelium [201]. Finally, passive transcellular diffusion is the last route of absorption of bioactive peptides into cells, which includes passive uptake into cells, intracellular transport, and basolateral secretion. In this pathway, also some characteristics of peptides, such as size, charge, and hydrophobicity, are effective in their transfer. It should be noted that due to the lack of identification of transport mediators in this pathway, it is impossible to quantify the transport of peptides through simple passive transcellular diffusion [192,204].

Therefore, understanding these factors and the transfer mechanisms of bioactive peptides helps to design efficient strategies for

enhancing bioavailability and preserving their bioactivities *in vivo*. For this purpose, we propose the following strategies, which hold great promise in this field.

1) Achieving bioactive peptides with high biostability by modifying the peptide structure or sequence (chemical or genetic), creating disulfide bridges, and cyclizing the peptide to apply conformational restrictions can lead to the unavailability of the cleavage sites for proteolytic enzymes [205]. It is important to note that these modifications should occur within the cleavage sites and with no changes in their bioactive properties. In addition, computational tools can be useful for investigating biostability, which is cost and time-effective. 2) Using suitable food matrices to deliver bioactive peptides to reduce adverse reactions and maintain the native structure of the peptides. Fiber-rich foods are recommended as an appropriate vehicle due to their limited reactivity [206]. 3) Using non-thermal food processing techniques such as pulsed electric field, ultrasound, ultrahigh hydrostatic pressure, and cold plasma to reduce unwanted reactions and prevent damage to the structure of bioactive peptides. 4) Encapsulation of bioactive peptides into nanosized colloidal delivery systems such as liposomes, biopolymer microgels, emulsions, and solid lipid nanoparticles to reduce the reaction with the food matrix, protect against harmful conditions of the GI tract and targeted release of bioactive peptides [207]. 5) Using penetration enhancers such as fatty acids, chitosan, and citric acid can help improve the bioavailability of bioactive peptides by facilitating the opening of tight junctions, growing membrane fluidity, and reducing mucus viscosity [208].

7. Conclusions and future perspectives

Bioactive peptides have drawn the interest of researchers due to their many physiological functions, which illustrate their potential for use in the pharmaceutical and food industries. These biomolecules can interact with diverse molecular targets and show effective therapeutic properties in health-related disorders, including cancer. This review provides an overview of bioactive peptides derived from various sources with anticancer properties to offer a valuable approach to improving human health. However, problems such as large-scale production, low biological stability due to passing through the gastrointestinal tract, interaction with the food matrix, and generally low bioavailability in the body make their use challenging and should be addressed. Therefore, we recommend that future research consider the strategies presented in this paper during the design of bioactive peptides to overcome the existing limitations. In addition, the anticancer activities of bioactive peptides have been shown mainly in cells and animal models. Hence, more clinical trials are required to evaluate safety, biostability, and bioavailability before exploitation for human consumption. On the other hand, despite extensive studies related to the identification of anticancer bioactive peptides, many natural sources still contain undiscovered and unknown compounds. The marine resources that comprise most of the earth are at the top of the candidate list that need further research. Recent advances in bioactive peptide technologies, such as their transformation strategies from waste to value-added ingredients and nanotechnology to encapsulate peptides in nanoparticles for controlled delivery and release, have a promising future in reducing production costs, scalability, and efficient production of bioactive peptides. As a result, the continuous exploration of anticancer bioactive peptides and the development of strategies to enhance their effectiveness can be a cost-effective alternative with limited side effects for high-risk chemotherapy drugs. Thanks to the advances made in the field of new therapeutic methods, cancer treatment is expected to become a manageable issue with limited complications.

CRediT authorship contribution statement

Maryam Bidram: Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Mohamad Reza Ganjalikhany:** Writing – review & editing, Supervision, Project administration, Methodology, Formal analysis, Conceptualization.

Data availability statement

Data included in article/supp. Material/referenced in the article.

Declaration of generative AI in scientific writing

The authors did not use any AI tools to during for the generation or analyzing the data in the manuscript.

Declaration of Competing interest

None.

References

[1] B. Spring, A.C. King, S.L. Pagoto, L. Van Horn, J.D. Fisher, Fostering multiple healthy lifestyle behaviors for primary prevention of cancer, Am. Psychol. 70 (2) (2015) 75. https://psycnet.apa.org/doi/10.1037/a0038806.
[2] A. Mehmood, L. Zhao, C. Wang, M. Nadeem, A. Raza, N. Ali, A.A. Shah, Management of hyperuricemia through dietary polyphenols as a natural medicament: a comprehensive review, Crit. Rev. Food Sci. Nutr. 59 (9) (2019) 1433–1455, https://doi.org/10.1080/10408398.2017.1412939.
[3] Cancer will kill 13.2 million a year by 2030: U.N, Retrieved from: https://www.reuters.com/article/us-cancer-global-idUSTRE6504H820100601, June 1, 2010.

[4] I.D.L. Cavalcanti, J.C.S. Soares, I.D.L. Cavalcanti, J.C.S. Soares, Conventional cancer treatment. Advances in Cancer Treatment: from Systemic Chemotherapy to Targeted Therapy, 2021, pp. 29–56, https://doi.org/10.1007/978-3-030-68334-4_4.

[5] A. Mustapha, A. Ismail, S.U. Abdullahi, O.N. Hassan, P.I. Ugwunnaji, E.B. Berinyuy, Cancer chemotherapy: a review update of the mechanisms of actions, prospects and associated problems, BIOMED Natural Appl. Sci. 1 (1) (2021) 1–19.

[6] A. Ulldemolins, J. Seras-Franzoso, F. Andrade, D. Rafael, I. Abasolo, P. Gener, Jr S. Schwartz, Perspectives of nano-carrier drug delivery systems to overcome cancer drug resistance in the clinics, Cancer Drug Resistance 4 (1) (2021) 44, https://doi.org/10.20517/cdr.2020.59.

[7] L. Wang, N. Wang, W. Zhang, X. Cheng, Z. Yan, G. Shao, C. Fu, Therapeutic peptides: current applications and future directions, Signal Transduct. Targeted Ther. 7 (1) (2022) 48, https://doi.org/10.1038/s41392-022-00904-4.

[8] M. Muttenthaler, G.F. King, D.J. Adams, P.F. Alewood, Trends in peptide drug discovery, Nat. Rev. Drug Discov. 20 (4) (2021) 309–325, https://doi.org/10.1038/s41573-020-00135-8.

[9] C.M. Li, P. Haratipour, R.G. Lingeman, J.J.P. Perry, L. Gu, R.J. Hickey, L.H. Malkas, Novel peptide therapeutic approaches for cancer treatment, Cells 10 (11) (2021) 2908, https://doi.org/10.3390/cells10112908.

[10] M. Akbarian, A. Khani, S. Eghbalpour, V.N. Uversky, Bioactive peptides: synthesis, sources, applications, and proposed mechanisms of action, Int. J. Mol. Sci. 23 (3) (2022) 1445, https://doi.org/10.3390/ijms23031445.

[11] J.M. Lorenzo, P.E. Munekata, B. Gómez, F.J. Barba, L. Mora, C. Pérez-Santaescolástica, F. Toldrá, Bioactive peptides as natural antioxidants in food products–A review, Trends Food Sci. Technol. 79 (2018) 136–147, https://doi.org/10.1016/j.tifs.2018.07.003.

[12] A. Mehmood, A. Iftikhar, X. Chen, Food-derived bioactive peptides with anti-hyperuricemic activity: a comprehensive review, Food Chem. 139444 (2024), https://doi.org/10.1016/j.foodchem.2024.139444.

[13] A. Mehmood, F. Pan, X. Ai, X. Tang, S. Cai, M.M. Soliman, L. Zhao, Novel angiotensin-converting enzyme (ACE) inhibitory mechanism of peptides from Macadamia integrifolia antimicrobial protein 2 (MiAMP2), J. Food Biochem. 46 (8) (2022) e14168, https://doi.org/10.1111/jfbc.14168.

[14] N. Ghadiri, M. Javidan, S. Sheikhi, Ö. Taştan, A. Parodi, Z. Liao, M. Ganjalıkhani-Hakemi, Bioactive peptides: an alternative therapeutic approach for cancer management, Front. Immunol. 15 (2024) 1310443, https://doi.org/10.3389/fimmu.2024.1310443.

[15] A. Sánchez, A. Vázquez, Bioactive peptides: a review, Food Quality and Safety 1 (1) (2017) 29–46, https://doi.org/10.1093/fqsafe/fyx006.

[16] E. Pojani, D. Barlocco, Romidepsin (FK228), A histone deacetylase inhibitor and its analogues in cancer chemotherapy, Curr. Med. Chem. 28 (7) (2021) 1290–1303, https://doi.org/10.2174/0929867327666200203113926.

[17] P. Smolewski, T. Robak, The discovery and development of romidepsin for the treatment of T-cell lymphoma, Expet Opin. Drug Discov. 12 (8) (2017) 859–873, https://doi.org/10.1080/17460441.2017.1341487.

[18] L. Wang, C. Dong, X. Li, W. Han, X. Su, Anticancer potential of bioactive peptides from animal sources, Oncol. Rep. 38 (2) (2017) 637–651, https://doi.org/10.3892/or.2017.5778.

[19] T.T. Nguyen, K. Heimann, W. Zhang, Protein recovery from underutilised marine bioresources for product development with nutraceutical and pharmaceutical bioactivities, Mar. Drugs 18 (8) (2020) 391, https://doi.org/10.3390/md18080391.

[20] I. Ahmed, M. Asgher, F. Sher, S.M. Hussain, N. Nazish, N. Joshi, H.M. Iqbal, Exploring marine as a rich source of bioactive peptides: challenges and opportunities from marine pharmacology, Mar. Drugs 20 (3) (2022) 208, https://doi.org/10.3390/md20030208.

[21] E. Talero, S. García-Mauriño, J. Ávila-Román, A. Rodríguez-Luna, A. Alcaide, V. Motilva, Bioactive compounds isolated from microalgae in chronic inflammation and cancer, Mar. Drugs 13 (10) (2015) 6152–6209, https://doi.org/10.3390/md13106152.

[22] C. Jo, F.F. Khan, M.I. Khan, J. Iqbal, Marine bioactive peptides: types, structures, and physiological functions, Food Rev. Int. 33 (1) (2017) 44–61, https://doi.org/10.1080/87559129.2015.1137311.

[23] R. Lemmens-Gruber, Antitumour effect of cyclodepsipeptides from marine sponges. Handbook of Anticancer Drugs from Marine Origin, 2015, pp. 101–111, https://doi.org/10.1007/978-3-319-07145-9_5.

[24] G. Taraboletti, M. Poli, R. Dossi, L. Manenti, P. Borsotti, G.T. Faircloth, R. Giavazzi, Antiangiogenic activity of aplidine, a new agent of marine origin, Br. J. Cancer 90 (12) (2004) 2418–2424, https://doi.org/10.1038/sj.bjc.6601864.

[25] M. Broggini, S.V. Marchini, E. Galliera, P. Borsotti, G. Taraboletti, E. Erba, M. d'Incalci, Aplidine, a new anticancer agent of marine origin, inhibits vascular endothelial growth factor (VEGF) secretion and blocks VEGF-VEGFR-1 (flt-1) autocrine loop in human leukemia cells MOLT-4, Leukemia 17 (1) (2003) 52–59, https://doi.org/10.1038/sj.leu.2402788.

[26] F. Gong, M.F. Chen, Y.Y. Zhang, C.Y. Li, C.X. Zhou, P.Z. Hong, Z.J. Qian, A novel peptide from abalone (Haliotis discus hannai) to suppress metastasis and vasculogenic mimicry of tumor cells and enhance anti-tumor effect in vitro, Mar. Drugs 17 (4) (2019) 244, https://doi.org/10.3390/md17040244.

[27] L. Su, G. Xu, J. Shen, Y. Tuo, X. Zhang, S. Jia, X. Su, Anticancer bioactive peptide suppresses human gastric cancer growth through modulation of apoptosis and the cell cycle, Oncol. Rep. 23 (1) (2010) 3–9, https://doi.org/10.3892/or_00000599.

[28] J.F. Hou, M.R. Yan, X.H. Yan, Y.N. Rong, T.M. Jiao, X.L. Su, Effect of anticancer bioactive peptide on leukemia mice, Acta Academiae Med Neimongol 26 (2004) 3–6.

[29] L.Y. Su, Y.X. Shi, M.R. Yan, Y. Xi, X.L. Su, Anticancer bioactive peptides suppress human colorectal tumor cell growth and induce apoptosis via modulating the PARP-p53-Mcl-1 signaling pathway, Acta Pharmacol. Sin. 36 (12) (2015) 1514–1519, https://doi.org/10.1038/aps.2015.80.

[30] Q. Yun, X. Su, X. Ouyang, Ouyang, Analysis of gene expression pattern in gallbladder carcinoma cells treated by anti-cancer bioactive pepetide (ACBP), China Prac Med 4 (2009) 10–12.

[31] Y.Y. Zhao, S.D. Peng, X.L. Su, Effects of anti-cancer bioactive peptide on cell cycle in human nasopharyngeal carcinoma strain CNE, Zhonghua er bi yan hou tou jing wai ke za zhi= Chinese journal of otorhinolaryngology head and neck surgery 41 (8) (2006) 607–611.

[32] H.X. Sun, L.Q. Chen, J. Zhang, F.Y. Chen, Anti-tumor and immunomodulatory activity of peptide fraction from the larvae of Musca domestica, J. Ethnopharmacol. 153 (3) (2014) 831–839, https://doi.org/10.1016/j.jep.2014.03.052.

[33] H. Van Zoggel, Y. Hamma-Kourbali, C. Galanth, A. Ladram, P. Nicolas, J. Courty, J. Delbé, Antitumor and angiostatic peptides from frog skin secretions, Amino Acids 42 (1) (2012) 385–395, https://doi.org/10.1007/s00726-010-0815-9.

[34] D. Shi, X. Hou, L. Wang, Y. Gao, D. Wu, X. Xi, C. Shaw, Two novel dermaseptin-like antimicrobial peptides with anticancer activities from the skin secretion of Pachymedusa dacnicolor, Toxins 8 (5) (2016) 144, https://doi.org/10.3390/toxins8050144.

[35] J.M. Conlon, D.C. Woodhams, H. Raza, L. Coquet, J. Leprince, T. Jouenne, L.A. Rollins-Smith, Peptides with differential cytolytic activity from skin secretions of the lemur leaf frog Hylomantis lemur (Hylidae: phyllomedusinae), Toxicon 50 (4) (2007) 498–506, https://doi.org/10.1016/j.toxicon.2007.04.017.

[36] M. Zhao, C. Wei, X. Yang, J. Zhou, J. Wang, F. Gu, Y. Qin, The milk-derived hexapeptide PGPIPN inhibits the invasion and migration of human ovarian cancer cells by regulating the expression of MTA1 and NM23H1 genes, Int. J. Oncol. 48 (4) (2016) 1721–1729, https://doi.org/10.3892/ijo.2016.3390.

[37] W. Chiangjong, J. Panachan, T. Vanichapol, N. Pongsakul, P. Pongphitcha, T. Siriboonpiputtana, S. Chutipongtanate, HMP-S7 is a novel anti-leukemic peptide discovered from human milk, Biomedicines 9 (8) (2021) 981, https://doi.org/10.3390/biomedicines9080981.

[38] J.H. Lee, H.D. Paik, Anticancer and immunomodulatory activity of egg proteins and peptides: a review, Poultry Sci. 98 (12) (2019) 6505–6516, https://doi.org/10.3382/ps/pez381.

[39] J.H. Lee, S.H. Moon, H.S. Kim, E. Park, D.U. Ahn, H.D. Paik, Antioxidant and anticancer effects of functional peptides from ovotransferrin hydrolysates, J. Sci. Food Agric. 97 (14) (2017) 4857–4864, https://doi.org/10.1002/jsfa.8356.

[40] J.D. Campeiro, M.P. Marinovic, F.C. Carapeto, C. Dal Mas, G.G. Monte, L. Carvalho Porta, M.A. Hayashi, Oral treatment with a rattlesnake native polypeptide crotamine efficiently inhibits the tumor growth with no potential toxicity for the host animal and with suggestive positive effects on animal metabolic profile, Amino Acids 50 (2) (2018) 267–278, https://doi.org/10.1007/s00726-017-2513-3.

[41] L.A. Moreira, L.P. Oliveira, M.R. Magalhães, S.A. Oliveira, J.R. Oliveira-Neto, P.M. Carvalho, L.C. Cunha, Acute toxicity, antinociceptive, and anti-inflammatory activities of the orally administered crotamine in mice, N. Schmied. Arch. Pharmacol. 394 (8) (2021) 1703–1711, https://doi.org/10.1007/s00210-021-02103-4.

[42] K. Saranya, V. Manivasagan, K. Gopi, K. Karthik, Broad-spectrum survey of medicinal plants as a potential source of anticancer agents, Bol. Latinoam. Caribe Plantas Med. Aromat. 21 (1) (2022), https://doi.org/10.37360/blacpma.22.21.1.01.
[43] C. Chaichana, A. Khamwut, J. Jaresitthikunchai, N. Phaonakrop, S. Ratanapo, S. Roytrakul, N.P. T-Thienprasert, A novel anti-cancer peptide extracted from Gynura pseudochina rhizome: cytotoxicity dependent on disulfide bond formation, Int. J. Pept. Res. Therapeut. 25 (2) (2019) 769–777, https://doi.org/10.1007/s10989-018-9726-5.
[44] H. Yuan, Z. Luo, Z. Ban, R.J. Reiter, Q. Ma, Z. Liang, L. Li, Bioactive peptides of plant origin: distribution, functionality, and evidence of benefits in food and health, Food Funct. 13 (6) (2022) 3133–3158, https://doi.org/10.1039/D1FO04077D.
[45] S. Ma, D. Huang, M. Zhai, L. Yang, S. Peng, C. Chen, M. Xu, Isolation of a novel bio-peptide from walnut residual protein inducing apoptosis and autophagy on cancer cells, BMC Compl. Alternative Med. 15 (1) (2015) 1–14, https://doi.org/10.1186/s12906-015-0940-9.
[46] V.P. Dia, H.B. Krishnan, BG-4, a novel anticancer peptide from bitter gourd (Momordica charantia), promotes apoptosis in human colon cancer cells, Sci. Rep. 6 (1) (2016) 1–12, https://doi.org/10.1038/srep33532.
[47] J.T. Li, J.L. Zhang, H. He, Z.L. Ma, Z.K. Nie, Z.Z. Wang, X.G. Xu, Apoptosis in human hepatoma HepG2 cells induced by corn peptides and its anti-tumor efficacy in H22 tumor bearing mice, Food Chem. Toxicol. 51 (2013) 297–305, https://doi.org/10.1016/j.fct.2012.09.038.
[48] A. Kannan, N.S. Hettiarachchy, J.O. Lay, R. Liyanage, Human cancer cell proliferation inhibition by a pentapeptide isolated and characterized from rice bran, Peptides 31 (9) (2010) 1629–1634, https://doi.org/10.1016/j.peptides.2010.05.018.
[49] S. Xu, Y. Shen, J. Xu, G. Qi, G. Chen, W. Wang, Y. Li, Antioxidant and anticancer effects in human hepatocarcinoma (HepG2) cells of papain-hydrolyzed sorghum kafirin hydrolysates, J. Funct.Foods 58 (2019) 374–382, https://doi.org/10.1016/j.jff.2019.05.016.
[50] N.D.C. Quintal-Bojórquez, L.M. Carrillo-Cocom, A.J. Hernández-Álvarez, M.R. Segura-Campos, Anticancer activity of protein fractions from chia (Salvia hispanica L.), J. Food Sci. 86 (7) (2021) 2861–2871, https://doi.org/10.1111/1750-3841.15780.
[51] J.H. Wong, T.B. Ng, Lunatusin, a trypsin-stable antimicrobial peptide from lima beans (Phaseolus lunatus L.), Peptides 26 (11) (2005) 2086–2092, https://doi.org/10.1016/j.peptides.2005.03.004.
[52] J.H. Wong, T.B. Ng, Vulgarinin, a broad-spectrum antifungal peptide from haricot beans (Phaseolus vulgaris), Int. J. Biochem. Cell Biol. 37 (8) (2005) 1626–1632, https://doi.org/10.1016/j.biocel.2005.02.022.
[53] C. Béné, M. Barange, R. Subasinghe, P. Pinstrup-Andersen, G. Merino, G.I. Hemre, M. Williams, Feeding 9 billion by 2050–Putting fish back on the menu, Food Secur. 7 (2015) 261–274, https://doi.org/10.1007/s12571-015-0427-z.
[54] J. O'Connor, M. Garcia-Vaquero, S. Meaney, B.K. Tiwari, Bioactive peptides from algae: traditional and novel generation strategies, structure-function relationships, and bioinformatics as predictive tools for bioactivity, Mar. Drugs 20 (5) (2022) 317, https://doi.org/10.3390/md20050317.
[55] X. Fan, L. Bai, X. Mao, X. Zhang, Novel peptides with anti-proliferation activity from the Porphyra haitanesis hydrolysate, Process Biochem. 60 (2017) 98–107, https://doi.org/10.1016/j.procbio.2017.05.018.
[56] S.C. Ko, S.Y. Heo, S.W. Choi, Z.J. Qian, S.J. Heo, D.H. Kang, W.K. Jung, A heptameric peptide isolated from the marine microalga Pavlova lutheri suppresses PMA-induced secretion of matrix metalloproteinase-9 through the inactivation of the JNK, p38, and NF-κB pathways in human fibrosarcoma cells, J. Appl. Phycol. 30 (2018) 2367–2378, https://doi.org/10.1007/s10811-018-1443-0.
[57] R. Singh, R. Das, S. Sangwan, B. Rohatgi, R. Khanam, S.P.G. Peera, S. Misra, Utilisation of agro-industrial waste for sustainable green production: a review, Environmental Sustainability 4 (4) (2021) 619–636, https://doi.org/10.1007/s42398-021-00200-x.
[58] FAO, Food wastage foot print impacts on natural resources, Available online: https://www.fao.org/news/story/en/item/196402/icode/. (Accessed 20 November 2022).
[59] N.P. Nirmal, A.C. Khanashyam, A.S. Mundanat, K. Shah, K.S. Babu, P. Thorakkattu, R. Pandiselvam, Valorization of fruit waste for bioactive compounds and their applications in the food industry, Foods 12 (3) (2023) 556, https://doi.org/10.3390/foods12030556.
[60] E.J. Rifna, N.N. Misra, M. Dwivedi, Recent advances in extraction technologies for recovery of bioactive compounds derived from fruit and vegetable waste peels: a review, Crit. Rev. Food Sci. Nutr. 63 (6) (2023) 719–752, https://doi.org/10.1080/10408398.2021.1952923.
[61] A.C. Lemes, L. Sala, J.D.C. Ores, A.R.C. Braga, M.B. Egea, K.F. Fernandes, A review of the latest advances in encrypted bioactive peptides from protein-rich waste, Int. J. Mol. Sci. 17 (6) (2016) 950, https://doi.org/10.3390/ijms17060950.
[62] M. Kumar, M. Tomar, D.J. Bhuyan, S. Punia, S. Grasso, A.G.A. Sa, M. Mekhemar, Tomato (Solanum lycopersicum L.) seed: a review on bioactives and biomedical activities, Biomed. Pharmacother. 142 (2021) 112018, https://doi.org/10.1016/j.biopha.2021.112018.
[63] R. Meral, Y.E. Kose, Z. Ceylan, İ. Cavidoglu, The potential use of agro-industrial by-products as sources of bioactive compounds: a nanotechnological approach, Stud. Nat. Prod. Chem. 73 (2022) 435–466, https://doi.org/10.1016/B978-0-323-91097-2.00014-5.
[64] R. Vásquez-Villanueva, L. Muñoz-Moreno, M.J. Carmena, M.L. Marina, M.C. García, In vitro antitumor and hypotensive activity of peptides from olive seeds, J. Funct.Foods 42 (2018) 177–184, https://doi.org/10.1016/j.jff.2017.12.062.
[65] V.H.S. Chang, D.H.A. Yang, H.H. Lin, G. Pearce, C.A. Ryan, Y.C. Chen, IbACP, a sixteen-amino-acid peptide isolated from Ipomoea batatas leaves, induces carcinoma cell apoptosis, Peptides 47 (2013) 148–156, https://doi.org/10.1016/j.peptides.2013.02.005.
[66] S.J. Rayaprolu, N.S. Hettiarachchy, P. Chen, A. Kannan, A. Mauromostakos, Peptides derived from high oleic acid soybean meals inhibit colon, liver and lung cancer cell growth, Food Res. Int. 50 (1) (2013) 282–288, https://doi.org/10.1016/j.foodres.2012.10.021.
[67] I.C. Sheih, T.J. Fang, T.K. Wu, P.H. Lin, Anticancer and antioxidant activities of the peptide fraction from algae protein waste, J. Agric. Food Chem. 58 (2) (2010) 1202–1207, https://doi.org/10.1021/jf903089m.
[68] R.G.G. Ortizo, V. Sharma, M.L. Tsai, J.X. Wang, P.P. Sun, P. Nargotra, C.D. Dong, Extraction of novel bioactive peptides from fish protein hydrolysates by enzymatic reactions, Appl. Sci. 13 (9) (2023) 5768, https://doi.org/10.3390/app13095768.
[69] Z. Yaghoubzadeh, F. Peyravii Ghadikolaii, H. Kaboosi, R. Safari, E. Fattahi, Antioxidant activity and anticancer effect of bioactive peptides from rainbow trout (Oncorhynchus mykiss) skin hydrolysate, Int. J. Pept. Res. Therapeut. 26 (1) (2020) 625–632, https://doi.org/10.1007/s10989-019-09869-5.
[70] A. Kandyliari, J.P. Golla, Y. Chen, N. Papandroulakis, M. Kapsokefalou, V. Vasiliou, Antiproliferative activity of protein hydrolysates derived from fish by-products on human colon and breast cancer cells, Proc. Nutr. Soc. 79 (OCE2) (2020) E282, https://doi.org/10.1017/S002966512000230X.
[71] E. Ilhan-Ayisigi, G. Budak, M.S. Celiktas, C. Sevimli-Gur, O. Yesil-Celiktas, Anticancer activities of bioactive peptides derived from rice husk both in free and encapsulated form in chitosan, J. Ind. Eng. Chem. 103 (2021) 381–391, https://doi.org/10.1016/j.jiec.2021.08.006.
[72] B. Wang, N. Xie, B. Li, Influence of peptide characteristics on their stability, intestinal transport, and in vitro bioavailability: a review, J. Food Biochem. 43 (1) (2019) e12571, https://doi.org/10.1111/jfbc.12571.
[73] Y. Huan, Q. Kong, H. Mou, H. Yi, Antimicrobial peptides: classification, design, application and research progress in multiple fields, Front. Microbiol. 11 (2020) 582779, https://doi.org/10.3389/fmicb.2020.582779.
[74] M. Arias, E.F. Haney, A.L. Hilchie, J.A. Corcoran, M.E. Hyndman, R.E. Hancock, H.J. Vogel, Selective anticancer activity of synthetic peptides derived from the host defence peptide tritrpticin, Biochim. Biophys. Acta Biomembr. 1862 (8) (2020) 183228, https://doi.org/10.1016/j.bbamem.2020.183228.
[75] S. Van Linthout, C. Tschöpe, Inflammation–cause or consequence of heart failure or both? Curr. Heart Fail. Rep. 14 (4) (2017) 251–265, https://doi.org/10.1007/s11897-017-0337-9.
[76] I. Cruz-Chamorro, G. Santos-Sánchez, C. Bollati, M. Bartolomei, J. Li, A. Arnoldi, C. Lammi, Hempseed (Cannabis sativa) peptides WVSPLAGRT and IGFLIIWV exert anti-inflammatory activity in the LPS-stimulated human hepatic cell line, J. Agric. Food Chem. 70 (2) (2022) 577–583, https://doi.org/10.1021/acs.jafc.1c07520.
[77] Y. Sheng, W.Y. Wang, M.F. Wu, Y.M. Wang, W.Y. Zhu, C.F. Chi, B. Wang, Eighteen novel bioactive peptides from monkfish (Lophius litulon) swim bladders: production, identification, antioxidant activity, and stability, Mar. Drugs 21 (3) (2023) 169, https://doi.org/10.3390/md21030169.
[78] Y. Song, L. Lei, X. Cai, H. Wei, C.Y. Yu, Immunomodulatory peptides for tumor treatment, Adv. Healthcare Mater. (2024) 2400512, https://doi.org/10.1002/adhm.202400512.
[79] M. Pavlicevic, N. Marmiroli, E. Maestri, Immunomodulatory peptides—a promising source for novel functional food production and drug discovery, Peptides 148 (2022) 170696, https://doi.org/10.1016/j.peptides.2021.170696.

[80] L. Wen, L. Huang, Y. Li, Y. Feng, Z. Zhang, Z. Xu, Y. Cheng, New peptides with immunomodulatory activity identified from rice proteins through peptidomic and in silico analysis, Food Chem. 364 (2021) 130357, https://doi.org/10.1016/j.foodchem.2021.130357.
[81] G.R. Dagenais, D.P. Leong, S. Rangarajan, F. Lanas, P. Lopez-Jaramillo, R. Gupta, S. Yusuf, Variations in common diseases, hospital admissions, and deaths in middle-aged adults in 21 countries from five continents (PURE): a prospective cohort study, Lancet 395 (10226) (2020) 785–794, https://doi.org/10.1016/S0140-6736(19)32007-0.
[82] F. Bray, M. Laversanne, H. Sung, J. Ferlay, R.L. Siegel, I. Soerjomataram, A. Jemal, Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA A Cancer J. Clin. 74 (3) (2024) 229–263, https://doi.org/10.3322/caac.21834.
[83] M. Yuan, Y. Zhao, H.T. Arkenau, T. Lao, L. Chu, Q. Xu, Signal pathways and precision therapy of small-cell lung cancer, Signal Transduct. Targeted Ther. 7 (1) (2022) 1–18, https://doi.org/10.1038/s41392-022-01013-y.
[84] T. Sawicki, M. Ruszkowska, A. Danielewicz, E. Niedźwiedzka, T. Arłukowicz, K.E. Przybyłowicz, A review of colorectal cancer in terms of epidemiology, risk factors, development, symptoms and diagnosis, Cancers 13 (9) (2021) 2025, https://doi.org/10.3390/cancers13092025.
[85] A. Barsouk, S.A. Padala, A. Vakiti, A. Mohammed, K. Saginala, K.C. Thandra, A. Barsouk, Epidemiology, staging and management of prostate cancer, Med. Sci. 8 (3) (2020) 28, https://doi.org/10.3390/medsci8030028.
[86] M. Bidram, Y. Zhao, N.G. Shebardina, A.V. Baldin, A.V. Bazhin, M.R. Ganjalikhany, M. Ganjalikhani-Hakemi, mRNA-based cancer vaccines: a therapeutic strategy for the treatment of melanoma patients, Vaccines 9 (10) (2021) 1060, https://doi.org/10.3390/vaccines9101060.
[87] M.T. Amjad, A. Chidharla, A. Kasi, Cancer chemotherapy (2020).
[88] D.T. Debela, S.G. Muzazu, K.D. Heraro, M.T. Ndalama, B.W. Mesele, D.C. Haile, T. Manyazewal, New Approaches and Procedures for Cancer Treatment: Current Perspectives, vol. 9, SAGE open medicine, 2021 20503121211034366, https://doi.org/10.1177/20503121211034366.
[89] M.S. Aslam, S. Naveed, A. Ahmed, Z. Abbas, I. Gull, M.A. Athar, Side effects of chemotherapy in cancer patients and evaluation of patients opinion about starvation based differential chemotherapy, J. Cancer Ther. 2014 (2014), https://doi.org/10.4236/jct.2014.58089.
[90] S. Aaghaz, V. Gohel, A. Kamal, Peptides as potential anticancer agents, Curr. Top. Med. Chem. 19 (17) (2019) 1491–1511, https://doi.org/10.2174/1568026619666190125161517.
[91] N. Quintal-Bojórquez, M.R. Segura-Campos, Bioactive peptides as therapeutic adjuvants for cancer, Nutr. Cancer 73 (8) (2021) 1309–1321, https://doi.org/10.1080/01635581.2020.1813316.
[92] A.S. Oguntade, F. Al-Amodi, A. Alrumayh, M. Alobaida, M. Bwalya, Anti-angiogenesis in cancer therapeutics: the magic bullet, J. Egypt. Natl. Cancer Inst. 33 (1) (2021) 1–11, https://doi.org/10.1186/s43046-021-00072-6.
[93] L. Zheng, P. Ling, Z. Wang, R. Niu, C. Hu, T. Zhang, X. Lin, A novel polypeptide from shark cartilage with potent anti-angiogenic activity, Cancer Biol. Ther. 6 (5) (2007) 775–780, https://doi.org/10.4161/cbt.6.5.4002.
[94] M. Simons, E. Gordon, L. Claesson-Welsh, Mechanisms and regulation of endothelial VEGF receptor signalling, Nat. Rev. Mol. Cell Biol. 17 (10) (2016) 611–625, https://doi.org/10.1038/nrm.2016.87.
[95] G. Liu, M. Liu, J. Wei, H. Huang, Y. Zhang, J. Zhao, X. Lin, CS5931, a novel polypeptide in Ciona savignyi, represses angiogenesis via inhibiting vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs), Mar. Drugs 12 (3) (2014) 1530–1544, https://doi.org/10.3390/md12031530.
[96] S.S. Senga, R.P. Grose, Hallmarks of cancer—the new testament, Open biology 11 (1) (2021) 200358, https://doi.org/10.1098/rsob.200358.
[97] C.M. Pfeffer, A.T. Singh, Apoptosis: a target for anticancer therapy, Int. J. Mol. Sci. 19 (2) (2018) 448, https://doi.org/10.3390/ijms19020448.
[98] C. Chatupheeraphat, S. Roytrakul, N. Phaonakrop, K. Deesrisak, S. Krobthong, U. Anurathapan, D. Tanyong, A novel peptide derived from ginger induces apoptosis through the modulation of p53, BAX, and BCL2 expression in leukemic cell lines, Planta Med. 87 (7) (2021) 560–569, https://doi.org/10.1055/a-1408-5629.
[99] X. Wan, H. Liu, Y. Sun, J. Zhang, X. Chen, N. Chen, Lunasin: a promising polypeptide for the prevention and treatment of cancer, Oncol. Lett. 13 (6) (2017) 3997–4001, https://doi.org/10.3892/ol.2017.6017.
[100] C.C. Hsieh, B. Hernández-Ledesma, B.O. De Lumen, Soybean peptide lunasin suppresses in vitro and in vivo 7, 12-dimethylbenz [a] anthracene-induced tumorigenesis, J. Food Sci. 75 (9) (2010) H311–H316, https://doi.org/10.1111/j.1750-3841.2010.01861.x.
[101] J.L. Díaz-Gómez, F. Castorena-Torres, R.E. Preciado-Ortiz, S. García-Lara, Anti-cancer activity of maize bioactive peptides, Front. Chem. 5 (2017) 44, https://doi.org/10.3389/fchem.2017.00044.
[102] M. Ortiz-Martinez, E.G. de Mejia, S. García-Lara, O. Aguilar, L.M. Lopez-Castillo, J.T. Otero-Pappatheodorou, Antiproliferative effect of peptide fractions isolated from a quality protein maize, a white hybrid maize, and their derived peptides on hepatocarcinoma human HepG2 cells, J. Funct.Foods 34 (2017) 36–48, https://doi.org/10.1016/j.jff.2017.04.015.
[103] S.A. dos Reis, L.L. da Conceição, M.M. e Dias, N.P. Siqueira, D.D. Rosa, L.L. de Oliveira, M.D.C.G. Peluzio, Kefir reduces the incidence of pre-neoplastic lesions in an animal model for colorectal cancer, J. Funct.Foods 53 (2019) 1–6, https://doi.org/10.1016/j.jff.2018.11.050.
[104] P. Sharma, H. Kaur, B.A. Kehinde, N. Chhikara, D. Sharma, A. Panghal, Food-derived anticancer peptides: a review, Int. J. Pept. Res. Therapeut. 27 (1) (2021) 55–70, https://doi.org/10.1007/s10989-020-10063-1.
[105] N. Avci, M. Hayar, O. Altmisdortoglu, O. Tanriverdi, A. Deligonul, C. Ordu, T. Evrensel, Smoking habits are an independent prognostic factor in patients with lung cancer, The Clinical Respiratory Journal 11 (5) (2017) 579–584, https://doi.org/10.1111/crj.12386.
[106] N. Duma, R. Santana-Davila, J.R. Molina, Non–small cell lung cancer: epidemiology, screening, diagnosis, and treatment, in: Mayo Clinic Proceedings, Elsevier, 2019, August, https://doi.org/10.1016/j.mayocp.2019.01.013.
[107] Z. Karami, S.H. Peighambardoust, J. Hesari, B. Akbari-Adergani, D. Andreu, Antioxidant, anticancer and ACE-inhibitory activities of bioactive peptides from wheat germ protein hydrolysates, Food Biosci. 32 (2019) 100450, https://doi.org/10.1016/j.fbio.2019.100450.
[108] Y. Ohsaki, A.F. Gazdar, H.C. Chen, B.E. Johnson, Antitumor activity of magainin analogues against human lung cancer cell lines, Cancer Res. 52 (13) (1992) 3534–3538.
[109] S. Jiang, Y. Jia, Y. Tang, D. Zheng, X. Han, F. Yu, G. Ding, Anti-proliferation activity of a decapeptide from perinereies aibuhitensis toward human lung cancer H1299 cells, Mar. Drugs 17 (2) (2019) 122, https://doi.org/10.3390/md17020122.
[110] N. Fakhri, M.A. Chad, M. Lahkim, A. Houari, H. Dehbi, A. Belmouden, N. El Kadmiri, Risk factors for breast cancer in women: an update review, Med. Oncol. 39 (12) (2022) 197, https://doi.org/10.1007/s12032-022-01804-x.
[111] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2019, CA A Cancer J. Clin. 69 (1) (2019) 7–34, https://doi.org/10.3322/caac.21551.
[112] Y.S. Sun, Z. Zhao, Z.N. Yang, F. Xu, H.J. Lu, Z.Y. Zhu, H.P. Zhu, Risk factors and preventions of breast cancer, Int. J. Biol. Sci. 13 (11) (2017) 1387.
[113] K.O. Sahna, B. Cakir, T. Tunali-Akbay, Antiproliferative activity of whey and casein bioactive peptides on breast cancer: an in vitro and in silico study, Int. J. Pept. Res. Therapeut. 28 (4) (2022) 1–12, https://doi.org/10.1007/s10989-022-10436-8.
[114] M.S. Taniya, M.V. Reshma, P.S. Shanimol, G. Krishnan, S. Priya, Bioactive peptides from amaranth seed protein hydrolysates induced apoptosis and antimigratory effects in breast cancer cells, Food Biosci. 35 (2020) 100588, https://doi.org/10.1016/j.fbio.2020.100588.
[115] Z. Xue, H. Wen, L. Zhai, Y. Yu, Y. Li, W. Yu, X. Kou, Antioxidant activity and anti-proliferative effect of a bioactive peptide from chickpea (Cicer arietinum L.), Food Res. Int. 77 (2015) 75–81, https://doi.org/10.1016/j.foodres.2015.09.027.
[116] I. Mármol, C. Sánchez-de-Diego, A. Pradilla Dieste, E. Cerrada, M.J. Rodriguez Yoldi, Colorectal carcinoma: a general overview and future perspectives in colorectal cancer, Int. J. Mol. Sci. 18 (1) (2017) 197, https://doi.org/10.3390/ijms18010197.
[117] S. Umayaparvathi, S. Meenakshi, V. Vimalraj, M. Arumugam, G. Sivagami, T. Balasubramanian, Antioxidant activity and anticancer effect of bioactive peptide from enzymatic hydrolysate of oyster (Saccostrea cucullata), Biomedicine & Preventive Nutrition 4 (3) (2014) 343–353, https://doi.org/10.1016/j.bionut.2014.04.006.
[118] S. Gogna, J. Kaur, K. Sharma, R. Prasad, J. Singh, V. Bhadariya, S. Jarial, Spirulina-an edible cyanobacterium with potential therapeutic health benefits and toxicological consequences, J. Am. Nutraceutical Assoc. 42 (6) (2023) 559–572, https://doi.org/10.1080/27697061.2022.2103852.
[119] Z. Wang, X. Zhang, Isolation and identification of anti-proliferative peptides from Spirulina platensis using three-step hydrolysis, J. Sci. Food Agric. 97 (3) (2017) 918–922, https://doi.org/10.1002/jsfa.7815.

[120] D.A.L. Vital, E.G. De Mejía, V.P. Dia, G. Loarca-Piña, Peptides in common bean fractions inhibit human colorectal cancer cells, Food Chem. 157 (2014) 347–355, https://doi.org/10.1016/j.foodchem.2014.02.050.
[121] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA A Cancer J. Clin. 68 (6) (2018) 394–424, https://doi.org/10.3322/caac.21492.
[122] R.C. Langan, Benign prostatic hyperplasia, Prim. Care Clin. Off. Pract. 46 (2) (2019) 223–232, https://doi.org/10.1016/j.pop.2019.02.003.
[123] B. Lumbreras, L.A. Parker, J.P. Caballero-Romeu, L. Gómez-Pérez, M. Puig-García, M. López-Garrigós, I. Hernández-Aguado, Variables associated with false-positive PSA results: a cohort study with real-world data, Cancers 15 (1) (2022) 261, https://doi.org/10.3390/cancers15010261.
[124] P. Guha, E. Kaptan, G. Bandyopadhyaya, S. Kaczanowska, E. Davila, K. Thompson, H. Ahmed, Cod glycopeptide with picomolar affinity to galectin-3 suppresses T-cell apoptosis and promotes cancer metastasis, Proc. Natl. Acad. Sci. USA 110 (13) (2013) 5052–5057, https://doi.org/10.1073/pnas.1202653110.
[125] F. Huang, Z. Yang, D. Yu, J. Wang, R. Li, G. Ding, Sepia ink oligopeptide induces apoptosis in prostate cancer cell lines via caspase-3 activation and elevation of Bax/Bcl-2 ratio, Mar. Drugs 10 (10) (2012) 2153–2165, https://doi.org/10.3390/md10102153.
[126] S. Guha, R.P. Ferrie, J. Ghimire, C.R. Ventura, E. Wu, L. Sun, W.C. Wimley, Applications and evolution of melittin, the quintessential membrane active peptide, Biochem. Pharmacol. 193 (2021) 114769, https://doi.org/10.1016/j.bcp.2021.114769.
[127] M.H. Park, M.S. Choi, D.H. Kwak, K.W. Oh, D.Y. Yoon, S.B. Han, J.T. Hong, Anti-cancer effect of bee venom in prostate cancer cells through activation of caspase pathway via inactivation of NF-κB, Prostate 71 (8) (2011) 801–812, https://doi.org/10.1002/pros.21296.
[128] M. Ceremuga, M. Stela, E. Janik, L. Gorniak, E. Synowiec, T. Sliwinski, M. Bijak, Melittin—a natural peptide from bee venom which induces apoptosis in human leukaemia cells, Biomolecules 10 (2) (2020) 247, https://doi.org/10.3390/biom10020247.
[129] D.D. Nikodijević, M.G. Milutinović, D.M. Cvetković, M.Đ. Ćupurdija, M.M. Jovanović, I.V. Mrkić, S.D. Marković, Impact of bee venom and melittin on apoptosis and biotransformation in colorectal carcinoma cell lines, Toxin Rev. 40 (4) (2021) 1272–1279, https://doi.org/10.1080/15569543.2019.1680564.
[130] P. Pandey, F. Khan, M.A. Khan, R. Kumar, T.K. Upadhyay, An updated review summarizing the anticancer efficacy of melittin from bee venom in several models of human cancers, Nutrients 15 (14) (2023) 3111, https://doi.org/10.3390/nu15143111.
[131] M.G. Davey, N. Miller, N.M. McInerney, A review of epidemiology and cancer biology of malignant melanoma, Cureus 13 (5) (2021).
[132] B. Domingues, J.M. Lopes, P. Soares, H. Pópulo, Melanoma treatment in review, ImmunoTargets Ther. 7 (2018) 35, https://doi.org/10.2147/ITT.S134842.
[133] R.A. Azevedo, A.K. Ferreira, A.V.V. Auada, K.F.M. Pasqualoto, R. Marques-Porto, D.A. Maria, I. Lebrun, Antitumor effect of cationic INKKI peptide from bovine β-casein on melanoma B16F10. https://doi.org/10.4236/jct.2012.34034, 2012.
[134] M.S. Libério, G.A. Joanitti, R.B. Azevedo, E.M. Cilli, L.C. Zanotta, A.C. Nascimento, M.S. Castro, Anti-proliferative and cytotoxic activity of pentadactylin isolated from Leptodactylus labyrinthicus on melanoma cells, Amino acids 40 (1) (2011) 51–59, https://doi.org/10.1007/s00726-009-0384-y.
[135] C. Shidal, N. Al-Rayyan, K. Yaddanapudi, K.R. Davis, Lunasin is a novel therapeutic agent for targeting melanoma cancer stem cells, Oncotarget 7 (51) (2016) 84128.
[136] S. Riedl, R. Leber, B. Rinner, H. Schaider, K. Lohner, D. Zweytick, Human lactoferricin derived di-peptides deploying loop structures induce apoptosis specifically in cancer cells through targeting membranous phosphatidylserine, Biochim. Biophys. Acta Biomembr. 1848 (11) (2015) 2918–2931, https://doi.org/10.1016/j.bbamem.2015.07.018.
[137] T.N. Soon, A.Y. Chia, W.H. Yap, Y.Q. Tang, Anticancer mechanisms of bioactive peptides, Protein Pept. Lett. 27 (9) (2020) 823–830, https://doi.org/10.2174/0929866527666200409102747.
[138] D.S.J. Ting, R.W. Beuerman, H.S. Dua, R. Lakshminarayanan, I. Mohammed, Strategies in translating the therapeutic potentials of host defense peptides, Front. Immunol. 11 (2020) 983, https://doi.org/10.3389/fimmu.2020.00983.
[139] A. Alghalayini, A. Garcia, T. Berry, C.G. Cranfield, The use of tethered bilayer lipid membranes to identify the mechanisms of antimicrobial peptide interactions with lipid bilayers, Antibiotics 8 (1) (2019) 12, https://doi.org/10.3390/antibiotics8010012.
[140] P. Kumar, J.N. Kizhakkedathu, S.K. Straus, Antimicrobial peptides: diversity, mechanism of action and strategies to improve the activity and biocompatibility in vivo, Biomolecules 8 (1) (2018) 4, https://doi.org/10.3390/biom8010004.
[141] Y. Lyu, G. Narsimhan, Antimicrobial peptides—membrane interactions, in: One Hundred Years of Colloid Symposia: Looking Back and Looking Forward, ACS Publications, 2023, https://doi.org/10.1021/bk-2023-1457.ch014.
[142] C.F. Le, C.M. Fang, S.D. Sekaran, Intracellular targeting mechanisms by antimicrobial peptides, Antimicrobial agents and chemotherapy 61 (4) (2017), https://doi.org/10.1128/aac.02340-16.
[143] J.C. Hsu, L.C. Lin, J.T. Tzen, J.Y. Chen, Pardaxin-induced apoptosis enhances antitumor activity in HeLa cells, Peptides 32 (6) (2011) 1110–1116, https://doi.org/10.1016/j.peptides.2011.04.024.
[144] B.S. Vad, K. Bertelsen, C.H. Johansen, J.M. Pedersen, T. Skrydstrup, N.C. Nielsen, D.E. Otzen, Pardaxin permeabilizes vesicles more efficiently by pore formation than by disruption, Biophys. J. 98 (4) (2010) 576–585, https://doi.org/10.1016/j.bpj.2009.08.063.
[145] H. Aghazadeh, H. Memariani, R. Ranjbar, K. Pooshang Bagheri, The activity and action mechanism of novel short selective LL-37-derived anticancer peptides against clinical isolates of Escherichia coli, Chem. Biol. Drug Des. 93 (1) (2019) 75–83, https://doi.org/10.1111/cbdd.13381.
[146] S. Jeyamogan, N.A. Khan, K. Sagathevan, R. Siddiqui, Sera/organ lysates of selected animals living in polluted environments exhibit cytotoxicity against cancer cell lines, Anti Cancer Agents Med. Chem. 19 (18) (2019) 2251–2268, https://doi.org/10.2174/1871520619666191011161314.
[147] K.C. Mulder, L.A. Lima, V.J. Miranda, S.C. Dias, O.L. Franco, Current scenario of peptide-based drugs: the key roles of cationic antitumor and antiviral peptides, Front. Microbiol. 4 (2013) 321, https://doi.org/10.3389/fmicb.2013.00321.
[148] S. Dadsena, C. Zollo, A.J. García-Sáez, Mechanisms of mitochondrial cell death, Biochem. Soc. Trans. 49 (2) (2021) 663–674, https://doi.org/10.1042/bst20200522.
[149] N. Van Opdenbosch, M. Lamkanfi, Caspases in cell death, inflammation, and disease, Immunity 50 (6) (2019) 1352–1364, https://doi.org/10.1016/j.immuni.2019.05.020.
[150] J. Yuan, D. Ofengeim, A guide to cell death pathways, Nat. Rev. Mol. Cell Biol. 25 (5) (2024) 379–395, https://doi.org/10.1038/s41580-023-00689-6.
[151] J.G. Valero, L. Sancey, J. Kucharczak, Y. Guillemin, D. Gimenez, J. Prudent, A. Aouacheria, Bax-derived membrane-active peptides act as potent and direct inducers of apoptosis in cancer cells, J. Cell Sci. 124 (4) (2011) 556–564, https://doi.org/10.1242/jcs.076745.
[152] L.M. Eike, N. Yang, Ø. Rekdal, B. Sveinbjørnsson, The oncolytic peptide LTX-315 induces cell death and DAMP release by mitochondria distortion in human melanoma cells, Oncotarget 6 (33) (2015) 34910.
[153] S. Bouchet, R. Tang, F. Fava, O. Legrand, B. Bauvois, The CNGRC-GG-D (KLAKLAK) 2 peptide induces a caspase-independent, Ca2+-dependent death in human leukemic myeloid cells by targeting surface aminopeptidase N/CD13, Oncotarget 7 (15) (2016) 19445.
[154] T. Bahmani, S. Sharifzadeh, G. Tamaddon, E. Farzadfard, F. Zare, M. Fadaie, A. Behzad-Behbahani, Mitochondrial targeted peptide (klaklak) 2, and its synergistic radiotherapy effects on apoptosis of radio resistant human monocytic leukemia cell line, Journal of biomedical physics & engineering 11 (2) (2021) 229.
[155] M. Capuozzo, M. Santorsola, M. Bocchetti, F. Perri, M. Cascella, V. Granata, A. Ottaiano, p53: from fundamental biology to clinical applications in cancer, Biology 11 (9) (2022) 1325, https://doi.org/10.3390/biology11091325.
[156] M. Vieler, S. Sanyal, p53 isoforms and their implications in cancer, Cancers 10 (9) (2018) 288, https://doi.org/10.3390/cancers10090288.
[157] H.E. Marei, A. Althani, N. Afifi, A. Hasan, T. Caceci, G. Pozzoli, C. Cenciarelli, p53 signaling in cancer progression and therapy, Cancer Cell Int. 21 (1) (2021) 1–15, https://doi.org/10.1186/s12935-021-02396-8.
[158] T. Yamada, K. Christov, A. Shilkaitis, L. Bratescu, A. Green, S. Santini, C.W. Beattie, p28, a first in class peptide inhibitor of cop1 binding to p53, Br. J. Cancer 108 (12) (2013) 2495–2504, https://doi.org/10.1038/bjc.2013.266.
[159] Y.F. Li, D.D. Wang, B.W. Zhao, W. Wang, C.Y. Huang, Y.M. Chen, Z.W. Zhou, High level of COP1 expression is associated with poor prognosis in primary gastric cancer, Int. J. Biol. Sci. 8 (8) (2012) 1168.
[160] Z. He, J. Lin, D. Peng, J. Zeng, X. Pan, R. Zheng, B. Du, Peptide fractions from Scha inchi induced apoptosis in HepG2 cells via P53 activation and a mitochondria-mediated pathway, J. Sci. Food Agric. (2023), https://doi.org/10.1002/jsfa.12845.

[161] J. Kulbacka, A. Choromańska, J. Rossowska, J. Weżgowiec, J. Saczko, M.P. Rols, Cell membrane transport mechanisms: ion channels and electrical properties of cell membranes. Transport across Natural and Modified Biological Membranes and its Implications in Physiology and Therapy, 2017, pp. 39–58, https://doi.org/10.1007/978-3-319-56895-9_3.
[162] J. Xia, H. Wang, S. Li, Q. Wu, L. Sun, H. Huang, M. Zeng, Ion channels or aquaporins as novel molecular targets in gastric cancer, Mol. Cancer 16 (1) (2017) 1–10, https://doi.org/10.1186/s12943-017-0622-y.
[163] N. Prevarskaya, R. Skryma, Y. Shuba, Ion channels in cancer: are cancer hallmarks oncochannelopathies? Physiol. Rev. 98 (2) (2018) 559–621, https://doi.org/10.1152/physrev.00044.2016.
[164] J.A. DeBin, J.E. Maggio, G.R. Strichartz, Purification and characterization of chlorotoxin, a chloride channel ligand from the venom of the scorpion, American journal of physiology-cell physiology 264 (2) (1993) C361–C369, https://doi.org/10.1152/ajpcell.1993.264.2.C361.
[165] S. Hong, M. Bi, L.E.I. Wang, Z. Kang, L. Ling, C. Zhao, CLC-3 channels in cancer, Oncol. Rep. 33 (2) (2015) 507–514, https://doi.org/10.3892/or.2014.3615.
[166] C.V. Bowen, D. DeBay, H.S. Ewart, P. Gallant, S. Gormley, T.T. Ilenchuk, J.M. Stewart, In vivo detection of human TRPV6-rich tumors with anti-cancer peptides derived from soricidin, PLoS One 8 (3) (2013) e58866, https://doi.org/10.1371/journal.pone.0058866.
[167] A.F. Räder, M. Weinmüller, F. Reichart, A. Schumacher-Klinger, S. Merzbach, C. Gilon, H. Kessler, Orally active peptides: is there a magic bullet? Angew. Chem. Int. Ed. 57 (44) (2018) 14414–14438, https://doi.org/10.1002/anie.201807298.
[168] A.L. Capriotti, G. Caruso, C. Cavaliere, R. Samperi, S. Ventura, R.Z. Chiozzi, A. Laganà, Identification of potential bioactive peptides generated by simulated gastrointestinal digestion of soybean seeds and soy milk proteins, J. Food Compos. Anal. 44 (2015) 205–213, https://doi.org/10.1016/j.jfca.2015.08.007.
[169] Y. Deng, L. Huang, C. Zhang, P. Xie, J. Cheng, X. Wang, L. Liu, Skin-care functions of peptides prepared from Chinese quince seed protein: sequences analysis, tyrosinase inhibition and molecular docking study, Ind. Crop. Prod. 148 (2020) 112331, https://doi.org/10.1016/j.indcrop.2020.112331.
[170] S. Chakrabarti, S. Guha, K. Majumder, Food-derived bioactive peptides in human health: challenges and opportunities, Nutrients 10 (11) (2018) 1738, https://doi.org/10.3390/nu10111738.
[171] K.F. Chai, A.Y.H. Voo, W.N. Chen, Bioactive peptides from food fermentation: a comprehensive review of their sources, bioactivities, applications, and future development, Compr. Rev. Food Sci. Food Saf. 19 (6) (2020) 3825–3885, https://doi.org/10.1111/1541-4337.12651.
[172] C. Chaves-López, A. Serio, A. Paparella, M. Martuscelli, A. Corsetti, R. Tofalo, G. Suzzi, Impact of microbial cultures on proteolysis and release of bioactive peptides in fermented milk, Food Microbiol. 42 (2014) 117–121, https://doi.org/10.1016/j.fm.2014.03.005.
[173] A.A. El-Fattah, S. Sakr, S. El-Dieb, H. Elkashef, Angiotensin-converting enzyme inhibition and antioxidant activity of commercial dairy starter cultures, Food Sci. Biotechnol. 25 (2016) 1745–1751, https://doi.org/10.1007/s10068-016-0266-5.
[174] M. Sharifi, A. Moridnia, D. Mortazavi, M. Salehi, M. Bagheri, A. Sheikhi, Kefir: a powerful probiotics with anticancer properties, Med. Oncol. 34 (2017) 1–7, https://doi.org/10.1007/s12032-017-1044-9.
[175] L. Wang, J. Zhang, Q. Yuan, H. Xie, J. Shi, X. Ju, Separation and purification of an anti-tumor peptide from rapeseed (Brassica campestris L.) and the effect on cell apoptosis, Food Funct. 7 (5) (2016) 2239–2248, https://doi.org/10.1039/C6FO00042H.
[176] P.G. Katsoyannis, Synthesis of Insulin: availability of A and B chains readily leads to the synthesis of this protein, Science 154 (3756) (1966) 1509–1514, https://doi.org/10.1126/science.154.3756.1509.
[177] D. Tymecka, A. Misicka, Solution phase peptide synthesis: the case of biphalin, Peptide Synthesis: Methods and Protocols (2020) 1–11, https://doi.org/10.1007/978-1-0716-0227-0_1.
[178] R.B. Merrifield, Solid phase peptide synthesis. I. The synthesis of a tetrapeptide, J. Am. Chem. Soc. 85 (14) (1963) 2149–2154, https://doi.org/10.1021/ja00897a025.
[179] F. Albericio, A. El-Faham, Choosing the right coupling reagent for peptides: a twenty-five-year journey, Org. Process Res. Dev. 22 (7) (2018) 760–772, https://doi.org/10.1021/acs.oprd.8b00159.
[180] S.B. Lawrenson, R. Arav, M. North, The greening of peptide synthesis, Green Chem. 19 (7) (2017) 1685–1691, https://doi.org/10.1039/C7GC00247E.
[181] W. Li, N.M. O'Brien-Simpson, M.A. Hossain, J.D. Wade, The 9-fluorenylmethoxycarbonyl (Fmoc) group in chemical peptide synthesis–its past, present, and future, Aust. J. Chem. 73 (4) (2019) 271–276, https://doi.org/10.1071/CH19427.
[182] Z. Wu, Y. Li, L. Zhang, Z. Ding, G. Shi, Microbial production of small peptide: pathway engineering and synthetic biology, Microb. Biotechnol. 14 (6) (2021) 2257–2278, https://doi.org/10.1111/1751-7915.13743.
[183] Y. Li, Recombinant production of antimicrobial peptides in Escherichia coli: a review, Protein Expr. Purif. 80 (2) (2011) 260–267, https://doi.org/10.1016/j.pep.2011.08.001.
[184] J. Zhou, X. Yang, W. Zhang, J. Wang, C. Wei, F. Gu, Y. Qin, Construction of an Anticancer Fusion Peptide (ACFP) derived from milk proteins and an assay of anti-ovarian cancer cells in vitro, Anti Cancer Agents Med. Chem. 17 (4) (2017) 635–643, https://doi.org/10.2174/1871520616666160627091131.
[185] R.J.S. de Castro, H.H. Sato, Biologically active peptides: processes for their generation, purification and identification and applications as natural additives in the food and pharmaceutical industries, Food Res. Int. 74 (2015) 185–198, https://doi.org/10.1016/j.foodres.2015.05.013.
[186] F. Khan, K. Niaz, M. Abdollahi, Toxicity of biologically active peptides and future safety aspects: an update, Curr. Drug Discov. Technol. 15 (3) (2018) 236–242, https://doi.org/10.2174/1570163815666180219112806.
[187] D. Bhandari, S. Rafiq, Y. Gat, P. Gat, R. Waghmare, V. Kumar, A review on bioactive peptides: physiological functions, bioavailability and safety, Int. J. Pept. Res. Therapeut. 26 (1) (2020) 139–150, https://doi.org/10.1007/s10989-019-09823-5.
[188] M. Silano, M. De Vincenzi, Bioactive antinutritional peptides derived from cereal prolamins: a review, Food Nahrung 43 (3) (1999) 175–184, https://doi.org/10.1002/(SICI)1521-3803(19990601)43:3<175::AID-FOOD175>3.0.CO;2-Z.
[189] R. Hartmann, J.M. Wal, H. Bernard, A.K. Pentzien, Cytotoxic and allergenic potential of bioactive proteins and peptides, Curr. Pharmaceut. Des. 13 (9) (2007) 897–920, https://doi.org/10.2174/138161207780414232.
[190] A.G. Abril, M. Pazos, T.G. Villa, P. Calo-Mata, J. Barros-Velázquez, M. Carrera, Proteomics characterization of food-derived bioactive peptides with anti-allergic and anti-inflammatory properties, Nutrients 14 (20) (2022) 4400, https://doi.org/10.3390/nu14204400.
[191] J. Carrasco-Castilla, A.J. Hernández-Álvarez, C. Jiménez-Martínez, G.F. Gutiérrez-López, G. Dávila-Ortiz, Use of proteomics and peptidomics methods in food bioactive peptide science and engineering, Food Eng. Rev. 4 (2012) 224–243, https://doi.org/10.1007/s12393-012-9058-8.
[192] X. Sun, C. Acquah, R.E. Aluko, C.C. Udenigwe, Considering food matrix and gastrointestinal effects in enhancing bioactive peptide absorption and bioavailability, J. Funct.Foods 64 (2020) 103680, https://doi.org/10.1016/j.jff.2019.103680.
[193] C.C. Udenigwe, R.O. Abioye, I.U. Okagu, J.I. Obeme-Nmom, Bioaccessibility of bioactive peptides: recent advances and perspectives, Curr. Opin. Food Sci. 39 (2021) 182–189, https://doi.org/10.1016/j.cofs.2021.03.005.
[194] P. Carsten Christophersen, M. Fano, L. Saaby, M. Yang, H. Mørck Nielsen, H. Mu, Characterization of particulate drug delivery systems for oral delivery of peptide and protein drugs, Curr. Pharmaceut. Des. 21 (19) (2015) 2611–2628, https://doi.org/10.2174/1381612821666150416100943.
[195] Y. Iwasaki, Y. Taga, A. Suzuki, M. Kurokawa, Y. Sato, Y. Shigemura, Effect of co-ingestion of collagen peptides with yogurt on blood absorption of short chain hydroxyproline peptides, Appl. Sci. 10 (12) (2020) 4066, https://doi.org/10.3390/app10124066.
[196] M. Ye, C. Zhang, L. Zhu, W. Jia, Q. Shen, Yak (Bos grunniens) bones collagen-derived peptides stimulate osteoblastic proliferation and differentiation via the activation of Wnt/β-catenin signaling pathway, J. Sci. Food Agric. 100 (6) (2020) 2600–2609, https://doi.org/10.1002/jsfa.10286.
[197] E.C. Li-Chan, Bioactive peptides and protein hydrolysates: research trends and challenges for application as nutraceuticals and functional food ingredients, Curr. Opin. Food Sci. 1 (2015) 28–37, https://doi.org/10.1016/j.cofs.2014.09.005.
[198] J.P. Kamdem, A. Tsopmo, Reactivity of peptides within the food matrix, J. Food Biochem. 43 (1) (2019) e12489, https://doi.org/10.1111/jfbc.12489.
[199] C.C. Udenigwe, V. Fogliano, Food matrix interaction and bioavailability of bioactive peptides: two faces of the same coin? J. Funct.Foods 35 (2017) 9–12, https://doi.org/10.1016/j.jff.2017.05.029.
[200] S. Senapati, S. Das, S.K. Batra, Mucin-interacting proteins: from function to therapeutics, Trends Biochem. Sci. 35 (4) (2010) 236–245, https://doi.org/10.1016/j.tibs.2009.10.003.

[201] Q. Xu, H. Hong, J. Wu, X. Yan, Bioavailability of bioactive peptides derived from food proteins across the intestinal epithelial membrane: a review, Trends Food Sci. Technol. 86 (2019) 399–411, https://doi.org/10.1016/j.tifs.2019.02.050.
[202] C. Wang, C. Chu, X. Ji, G. Luo, C. Xu, H. He, Y. Jin, Biology of peptide transporter 2 in mammals: new insights into its function, structure and regulation, Cells 11 (18) (2022) 2874, https://doi.org/10.3390/cells11182874.
[203] T. Matsui, Are peptides absorbable compounds? J. Agric. Food Chem. 66 (2) (2017) 393–394, https://doi.org/10.1021/acs.jafc.7b05589.
[204] M. Miguel, A. Davalos, M.A. Manso, G. de la Pena, M.A. Lasunción, R. López-Fandiño, Transepithelial transport across Caco-2 cell monolayers of antihypertensive egg-derived peptides. PepT1-mediated flux of Tyr-Pro-Ile, Mol. Nutr. Food Res. 52 (12) (2008) 1507–1513, https://doi.org/10.1002/mnfr.200700503.
[205] M. Oba, Y. Nagano, T. Kato, M. Tanaka, Secondary structures and cell-penetrating abilities of arginine-rich peptide foldamers, Sci. Rep. 9 (1) (2019) 1349, https://doi.org/10.1038/s41598-018-38063-8.
[206] X. Sun, C.C. Udenigwe, Chemistry and biofunctional significance of bioactive peptide interactions with food and gut components, J. Agric. Food Chem. 68 (46) (2020) 12972–12977, https://doi.org/10.1021/acs.jafc.9b07559.
[207] D.J. McClements, Encapsulation, protection, and delivery of bioactive proteins and peptides using nanoparticle and microparticle systems: a review, Adv. Colloid Interface Sci. 253 (2018) 1–22, https://doi.org/10.1016/j.cis.2018.02.002.
[208] J. Renukuntla, A.D. Vadlapudi, A. Patel, S.H. Boddu, A.K. Mitra, Approaches for enhancing oral bioavailability of peptides and proteins, Int. J. Pharm. 447 (1–2) (2013) 75–93, https://doi.org/10.1016/j.ijpharm.2013.02.030.
[209] C.F. Chi, F.Y. Hu, B. Wang, T. Li, G.F. Ding, Antioxidant and anticancer peptides from the protein hydrolysate of blood clam (Tegillarca granosa) muscle, J. Funct.Foods 15 (2015) 301–313, https://doi.org/10.1016/j.jff.2015.03.045.
[210] E.K. Kim, Y.S. Kim, J.W. Hwang, J.S. Lee, S.H. Moon, B.T. Jeon, P.J. Park, Purification and characterization of a novel anticancer peptide derived from Ruditapes philippinarum, Process Biochem. 48 (7) (2013) 1086–1090, https://doi.org/10.1016/j.procbio.2013.05.004.
[211] P. Zhang, Y. Yan, J. Wang, X. Dong, G. Zhang, Y. Zeng, Z. Liu, An anti-cancer peptide LVTX-8 inhibits the proliferation and migration of lung tumor cells by regulating causal genes' expression in p53-related pathways, Toxins 12 (6) (2020) 367, https://doi.org/10.3390/toxins12060367.
[212] S.F. Zhang, Z. Chen, Melittin exerts an antitumor effect on non-small cell lung cancer cells, Mol. Med. Rep. 16 (3) (2017) 3581–3586, https://doi.org/10.3892/mmr.2017.6970.
[213] R. Teta, E. Irollo, G. Della Sala, G. Pirozzi, A. Mangoni, V. Costantino, Smenamides A and B, chlorinated peptide/polyketide hybrids containing a dolapyrrolidinone unit from the Caribbean sponge Smenospongia aurea. Evaluation of their role as leads in antitumor drug research, Mar. Drugs 11 (11) (2013) 4451–4463, https://doi.org/10.3390/md11114451.
[214] Z. Wang, X. Zhang, Inhibitory effects of small molecular peptides from Spirulina (Arthrospira) platensis on cancer cell growth, Food Funct. 7 (2) (2016) 781–788, https://doi.org/10.1039/C5FO01186H.
[215] C.C. Hung, Y.H. Yang, P.F. Kuo, K.C. Hsu, Protein hydrolysates from tuna cooking juice inhibit cell growth and induce apoptosis of human breast cancer cell line MCF-7, J. Funct.Foods 11 (2014) 563–570, https://doi.org/10.1016/j.jff.2014.08.015.
[216] S.K. Lam, T.B. Ng, Apoptosis of human breast cancer cells induced by hemagglutinin from Phaseolus vulgaris cv. Legumi secchi, Food Chem. 126 (2) (2011) 595–602, https://doi.org/10.1016/j.foodchem.2010.11.049.
[217] K.C. Hsu, E.C. Li-Chan, C.L. Jao, Antiproliferative activity of peptides prepared from enzymatic hydrolysates of tuna dark muscle on human breast cancer cell line MCF-7, Food Chem. 126 (2) (2011) 617–622, https://doi.org/10.1016/j.foodchem.2010.11.066.
[218] Q. Zheng, D. Qiu, X. Liu, L. Zhang, S. Cai, X. Zhang, Antiproliferative effect of Dendrobium catenatum Lindley polypeptides against human liver, gastric and breast cancer cell lines, Food Funct. 6 (5) (2015) 1489–1495, https://doi.org/10.1039/C5FO00060B.
[219] S. Li, L. Hao, W. Bao, P. Zhang, D. Su, Y. Cheng, Y. Yang, A novel short anionic antibacterial peptide isolated from the skin of Xenopus laevis with broad antibacterial activity and inhibitory activity against breast cancer cell, Arch. Microbiol. 198 (5) (2016) 473–482, https://doi.org/10.1007/s00203-016-1206-8.
[220] M.D. Verenhitach, L.G. de Sousa Cabral, R.C.B. Alves, D.A. Maria, Evaluation of the antitumor and antiproliferative effects of the INKKI peptide on MCF-7 breast adenocarcinoma cells, Int J Herb Med 8 (1) (2020) 46–53.
[221] C.C. Hsieh, B. Hernández-Ledesma, B.O. De Lumen, Lunasin, a novel seed peptide, sensitizes human breast cancer MDA-MB-231 cells to aspirin-arrested cell cycle and induced apoptosis, Chem. Biol. Interact. 186 (2) (2010) 127–134, https://doi.org/10.1016/j.cbi.2010.04.027.
[222] A. Kuerban, A.L. Al-Malki, T.A. Kumosani, R.A. Sheikh, F.A.M. Al-Abbasi, F.A. Alshubaily, S. Salama Moselhy, Identification, protein antiglycation, antioxidant, antiproliferative, and molecular docking of novel bioactive peptides produced from hydrolysis of Lens culinaris, J. Food Biochem. 44 (12) (2020) e13494, https://doi.org/10.1111/jfbc.13494.
[223] R. Vilcacundo, B. Miralles, W. Carrillo, B. Hernández-Ledesma, In vitro chemopreventive properties of peptides released from quinoa (Chenopodium quinoa Willd.) protein under simulated gastrointestinal digestion, Food Res. Int. 105 (2018) 403–411, https://doi.org/10.1016/j.foodres.2017.11.036.
[224] V.P. Dia, E.G. De Mejia, Lunasin induces apoptosis and modifies the expression of genes associated with extracellular matrix and cell adhesion in human metastatic colon cancer cells, Mol. Nutr. Food Res. 55 (4) (2011) 623–634, https://doi.org/10.1002/mnfr.201000419.
[225] Jumeri, S.M. Kim, Antioxidant and anticancer activities of enzymatic hydrolysates of solitary tunicate (Styela clava), Food Sci. Biotechnol. 20 (4) (2011) 1075–1085, https://doi.org/10.1007/s10068-011-0146-y.
[226] R. Song, R.B. Wei, H.Y. Luo, Z.S. Yang, Isolation and identification of an antiproliferative peptide derived from heated products of peptic hydrolysates of half-fin anchovy (Setipinna taty), J. Funct.Foods 10 (2014) 104–111, https://doi.org/10.1016/j.jff.2014.06.010.
[227] Z.Z. Wu, G.F. Ding, F.F. Huang, Z.S. Yang, F.M. Yu, Y.P. Tang, R. Chen, Anticancer activity of anthopleura anjunae oligopeptides in prostate cancer DU-145 cells, Mar. Drugs 16 (4) (2018) 125, https://doi.org/10.3390/md16040125.
[228] H. Shen, Y. Xie, S. Ye, K. He, L. Yi, R. Cui, Spider peptide toxin lycosin-I induces apoptosis and inhibits migration of prostate cancer cells, Exp. Biol. Med. 243 (8) (2018) 725–735, https://doi.org/10.1177/1535370218772802.
[229] N.M. Almansour, E. Pirogova, P.J. Coloe, I. Cosic, T.S. Istivan, A bioactive peptide analogue for myxoma virus protein with a targeted cytotoxicity for human skin cancer in vitro, J. Biomed. Sci. 19 (1) (2012) 1–13, https://doi.org/10.1186/1423-0127-19-65.
[230] A. Pereira, A. Kerkis, M.A. Hayashi, A.S. Pereira, F.S. Silva, E.B. Oliveira, I. Kerkis, Crotamine toxicity and efficacy in mouse models of melanoma, Expet Opin. Invest. Drugs 20 (9) (2011) 1189–1200, https://doi.org/10.1517/13543784.2011.602064.
[231] H. Wang, M. Ke, Y. Tian, J. Wang, B. Li, Y. Wang, C. Zhou, BF-30 selectively inhibits melanoma cell proliferation via cytoplasmic membrane permeabilization and DNA-binding in vitro and in B16F10-bearing mice, Eur. J. Pharmacol. 707 (1–3) (2013) 1–10, https://doi.org/10.1016/j.ejphar.2013.03.028.
[232] C. Wodlej, S. Riedl, B. Rinner, R. Leber, C. Drechsler, D.R. Voelker, D. Zweytick, Interaction of two antitumor peptides with membrane lipids–Influence of phosphatidylserine and cholesterol on specificity for melanoma cells, PLoS One 14 (1) (2019), https://doi.org/10.1371/journal.pone.0211187.
[233] S. Sangboonruang, K. Kitidee, P. Chantawannakul, K. Tragoolpua, Y. Tragoolpua, Melittin from Apis florea venom as a promising therapeutic agent for skin cancer treatment, Antibiotics 9 (8) (2020) 517, https://doi.org/10.3390/antibiotics9080517.
[234] F. Li, S. Wu, N. Chen, J. Zhu, X. Zhao, P. Zhang, Z. Liu, Fatty acid modification of the anticancer peptide LVTX-9 to enhance its cytotoxicity against malignant melanoma cells, Toxins 13 (12) (2021) 867, https://doi.org/10.3390/toxins13120867.