



Recent advances of bioactive proteins/polypeptides in the treatment of breast cancer

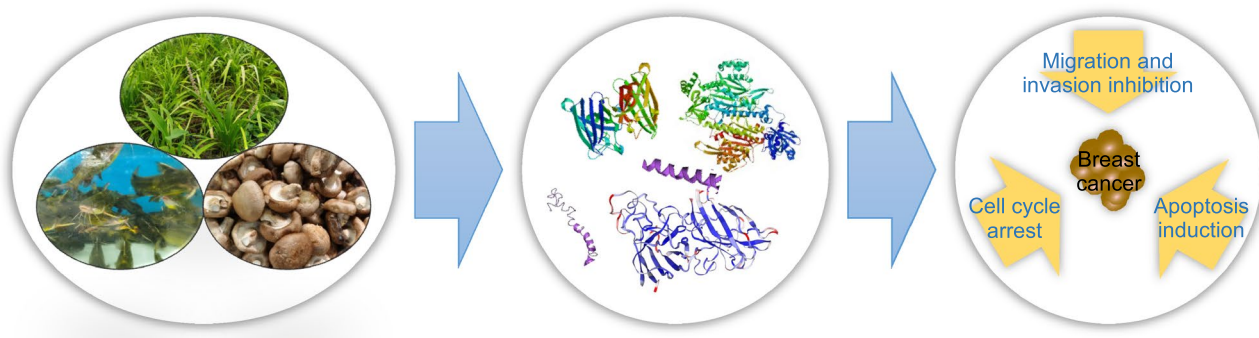
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Abstract

Proteins do not only serve as nutrients to fulfill the demand for food, but also are used as a source of bioactive proteins/polypeptides for regulating physical functions and promoting physical health. Female breast cancer has the highest incidence in the world and is a serious threat to women's health. Bioactive proteins/polypeptides exert strong anti-tumor effects and exhibit inhibition of multiple breast cancer cells. This review discussed the suppressing effects of bioactive proteins/polypeptides on breast cancer in vitro and in vivo, and their mechanisms of migration and invasion inhibition, apoptosis induction, and cell cycle arrest. This may contribute to providing a basis for the development of bioactive proteins/polypeptides for the treatment of breast cancer.

Graphical abstract



Keywords Bioactive proteins · Bioactive polypeptides · Breast cancer · Inhibition · Mechanisms

Introduction

Proteins are one of the main nutrients for the requirement of humans and possess functions of promoting growth and development, strengthening immunity, and being involved in

metabolism (Kitada et al., 2019). Some special proteins also have particular abilities, such as anti-tumor, immunomodulation, anti-oxidant, and anti-thrombosis, and are termed bioactive proteins (Auestad and Layman, 2021). Proteins are hydrolyzed to polypeptides. These polypeptides commonly contain 2–30 amino acids and have multiple functions determined by their amino acid sequence, being called bioactive polypeptides (Chakrabarti et al., 2018; Chelliah et al., 2021). They have good health effects such as lowering blood pressure, antibacterial activity, anti-tumor, and anti-inflammation. It has been found that bioactive proteins/polypeptides have remarkable anti-tumor effects. For example,

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fungal immunomodulatory proteins (FIPs) are a kind of bioactive proteins from fungi such as *Ganoderma lucidum* and *Flammulina velutipes* (Li et al., 2010a, 2011a), and have inhibitory effects against multiple cancer cells such as gastric, liver and breast cancer cells (Li et al., 2011b, 2019b).

Cancer is a major health problem in the world. Breast cancer is the most commonly diagnosed cancer with 2.26 million new cases worldwide in 2020 (Ferlay et al., 2021). Despite some clinical success, high incidence of recurrence and metastasis still lead to high mortality in breast cancer patients (Akram et al., 2017). Some chemotherapeutic drugs with high doses have serious side effects and drug resistance in the therapy of breast cancer (Al-Mahmood et al., 2018). Thus, it is of great importance to discover and identify more effective agents with fewer side effects (Hu et al., 2019). Natural products are a precious resource for developing and discovering antitumor drugs due to multi-targeting efficacy, no toxicity, and no drug resistance (Hashem et al., 2022; Ullah et al., 2022). Moreover, it has been demonstrated that naturally bioactive products possess abilities in the prevention and treatment of breast cancer (Bak et al., 2016). This review aims to discuss the potential of bioactive proteins/polypeptides in the prevention and treatment of breast cancer.

Acquirement of bioactive proteins/polypeptides

Proteins and polypeptides are the material basis of life. Bioactive proteins/polypeptides are special proteins and polypeptides with particular physiological functions. Bioactive proteins/polypeptides originate mainly from meat, milk, cereal, fish, seaweeds, vegetables, and fungi (Kaur et al., 2021). The most common methods to produce proteins/polypeptides include enzyme hydrolysis and microbial fermentation (Daliri et al., 2017). Besides, a PepSAVI-MS (statistically-guided bioactive peptides prioritized via mass spectrometry) pipeline is developed for bioactive peptide discovery (Kirkpatrick et al., 2017). Using this pipeline, some bioactive peptides are successfully identified from biological species such as *Enterococcus faecalis* (Kirkpatrick et al., 2018b), *Ustilago maydis* (Kirkpatrick et al., 2018a), *Viola odorata* (Parsley et al., 2018) and *Amaranthus tricolor* (Moyer et al., 2019).

Mechanism of breast cancer suppression by bioactive proteins/polypeptides

Bioactive proteins/polypeptides have potential medicinal values, especially anti-tumor effects (Li et al., 2011b; Wu et al., 2014). Some bioactive proteins/polypeptides from

plants, animals, and microbes can inhibit breast cancer cell growth (Tables 1 and 2) based on mechanisms of migration and invasion inhibition, apoptosis induction, and cell cycle arrest (Fig. 1).

Inhibition of migration and invasion

Cancer cells are capable of migration and invasion to spread within tissues (Chambers et al., 2002). Mechanisms of the migration include extracellular matrix (ECM) degradation, which needs corresponding enzymes, such as matrix metalloproteinases (MMPs) (Alaseem et al., 2019). MMPs are zinc-dependent endopeptidases and contribute to the pathogenesis of various diseases (Bassiouni et al., 2021). Platelet endothelial cell adhesion molecule-1 (PECAM-1 or CD31) is a 130-kDa highly glycosylated transmembrane member of the Ig superfamily (Caligiuri, 2020) and mediates cancer metastasis by activating integrins (Zhang et al., 2018). Tetraspanins CD151, a transmembrane 4 superfamily protein, regulate the epidermal growth factor receptor (EGFR)/focal adhesion kinase (FAK) signaling pathway by affecting integrins (Zhu et al., 2021). Integrins comprise a family of 24 heterodimeric receptors formed by 18 α -subunits and eight β -subunits (Desgrosellier and Chersesh, 2010). Distinct integrin heterodimers are in specific cancer cells. For example, $\alpha 6 \beta 4$ and $\alpha \nu \beta 3$ are expressed in breast cancer. Integrins bind to ECM proteins and activate the FAK and proto-oncogene tyrosine-protein kinase Src (Src) family kinase (SFK) signaling, then impinging on the rat sarcoma virus (Ras)/extracellular signal-regulated kinases (ERK) and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathways (Cooper and Giancotti, 2019). The pathways contribute to the regulation of nuclear factor-kappaB (NF- κ B) activity (Mali et al., 2018; Mao et al., 2019), promoting the expressions of MMP-2 (Tao et al., 2018), -7 (Liu et al., 2017a) and -9 (Tan et al., 2022). Iturin A is a lipopeptide consisting of a hydrophilic peptide moiety linked to a hydrophobic fatty acid chain and is purified from a marine bacterium *Bacillus megaterium* (Dey et al., 2015). Zhang et al. isolated water-soluble polypeptides from a traditional Chinese pharmaceutical and functional food *Pilose antler*, named PAWPs (Zheng et al., 2020). In xenograft models, both iturin A and PAWPs reduce CD31 expression, leading to metastasis inhibition (Dey et al., 2015; Zheng et al., 2020). An important characteristic of iturin A is amphiphilic. Zhao et al. found that the hydrophilic peptide (NYNQPNs) showed no effect on HepG2 cells proliferation, suggesting that the fatty acid chain plays an important role in its activity (Zhao et al., 2021). Using the FireDock web server and immunoprecipitation assay, it is found that a marine natural metabolite Cyclo (L-Leucyl-L-Prolyl) peptide (CLP) from *Streptomyces mangrovisoli* has a strong interaction with CD151 and

Table 1 Anti-tumor and other activities of bioactive proteins/polypeptides in the cell models of human breast cancer

| Source | Name or type | Molecular weight | Cell models | Antiproliferation (IC ₅₀) | Potential target proteins | Other bioactivities | References |
|--------------------------------|---------------|------------------|-------------|--|------------------------------|--|---|
| <i>Acacia confusa</i> | Protein | 70 kDa (Dimer) | MCF-7 | 10.7 μM (48 h) | – | Anti-HIV-1 | Lam and Ng (2010) |
| <i>Brassica para-chinensis</i> | Brassicaparin | 5716 Da | MCF-7 | 4.8 μM (72 h) | – | Anti-fungi, anti-HIV-1 | Lin and Ng (2009) |
| <i>Cicer arietinum</i> | CPe-III | 1155 Da | MCF-7 | 2.38 μmol/mL (72 h) § | p53 | Anti-oxidation, lowering lipid | Xue et al. (2015, 2018) |
| | | | MDA-MB-231 | 1.50 μmol/mL (72 h) § | – | – | – |
| <i>Dendrobium catenatum</i> | P1 | 1416.8370 Da | MCF-7 | 500 μg/mL (30–41.8%, 48 h) † | – | – | Zheng et al. (2015) |
| | P2 | 2993.7427 Da | | | | | |
| | P3 | 1503.8099 Da | | | | | |
| <i>Fagopyrum tataricum</i> | TBWSP31 | – | Bcap37 | – | – | – | Guo et al. (2010) |
| <i>Glycine max</i> | MAPF | > 10 kDa | MDA-MB-231 | 15.19 mg/mL | – | Anti-oxidation | Marcela et al. (2016) |
| | | | MCF-7 | 19.99 mg/mL | – | – | – |
| | Hydrolysate | 5–10 kDa | MCF-7 | 654 μg/mL | – | – | Rayaprolu et al. (2017) |
| | Lunasin | 5.5 kDa | MCF-7 | 508.6 μM (24 h); 431.9 μM (48 h) | αvβ3 integrin, α5β1 integrin | Anti-oxidation, anti-inflammation | Hernandez-Ledesma et al. (2009), Dia and Gonzalez de Mejia (2011), Cam and de Mejia (2012), Jiang et al. (2016) |
| <i>Gynura procumbens</i> | SN-F11/12 | – | MDA-MB-231 | 224.7 μM (24 h); 194.9 μM (48 h) | – | – | Hew et al. (2013) |
| <i>Juglans regia</i> | Hydrolysate | – | MDA-MB-231 | 650 μg/mL | – | Anti-oxidation | Jahanbani et al. (2016) |
| | CTLEW | 651.2795 Da | MCF-7 | 0.449 mg/mL (48 h) | – | – | Ma et al. (2015) |
| | Hydrolysate | <5 kDa | | 3.64 mg/mL | – | Anti-oxidation | Xu (2014) |
| <i>Momordica balsamina</i> | Balsamin | 28 kDa | MCF-7 | 179.47 μg/mL (24 h); 49.40 μg/mL (48 h); 24.53 μg/mL (72 h) | – | DNase, anti-oxidation, anti-bacteria, anti-HIV-1 | Kaur et al. (2013), Aji et al. (2016, 2017) |
| | | | BT549 | 399.41 μg/mL (24 h); 103.54 μg/mL (48 h); 32.79 μg/mL (72 h) | – | – | – |
| Rice bran | EQRR | 685.378 Da | MCF-7 | 1,000 μg/mL (80%, 24 h) † | – | Anti-covid-19 | Kannan et al. (2010), Gasmov et al. (2021) |
| | | | MDA-MB-231 | – | – | – | – |

Table 1 (continued)

| Source | Name or type | Molecular weight | Cell models | Antiproliferation (IC ₅₀) | Potential target proteins | Other bioactivities | References |
|----------------------------|------------------------------|------------------|-------------|--|---|---|---|
| Wheat germ | WGWSP11 | 41 kDa | MDA-MB-231 | 76.35 µg/mL (24 h); 22.33 µg/mL (48 h); 14.41 µg/mL (72 h) | – | – | Zhou et al. (2013) |
| <i>Viola odorata</i> | CyO8 | 3,225.42 Da | MDA-MB-231 | 1.15 µM (24 h) | – | Anti-fungi | Parsley et al. (2018) |
| <i>Withania somnifera</i> | WSPF | 41 and 21 kDa | MDA-MB-231 | 92 µg/mL (72 h) | – | – | Dar et al. (2019) |
| <i>Zea mays</i> | MzDef | 4 kDa | MCF-7 | 14.85 µg/mL (24 h) | – | Anti-bacteria, anti-fungi | Al Kashgry et al. (2020) |
| <i>Agkistrodon acutus</i> | W1 | 443 Da | MDA-MB-231 | 10 µg/mL (31.0%, 24 h) † | – | – | Wu et al. (2012) |
| | W2 | 429 Da | | 10 µg/mL (27.7%, 24 h) † | – | – | |
| | W3 | 443 Da | | 10 µg/mL (61.1%, 24 h) † | – | – | |
| | venom | – | | 1.267 mg/L (48 h) | – | – | Zeng et al. (2022) |
| <i>Alburnus tarichi</i> | Roe protein hydrolysate | – | MDA-MB-231 | 1.81 µg/mL (48 h) | – | – | Berkoz et al. (2020) |
| | HN-1 | 2278.9 Da | MCF-7 | 1.89 µg/mL (48 h) | – | – | |
| <i>Amolops hainanensis</i> | | | MCF-7 | 6.97 µM (48 h) | – | Immunomodulation | Qiao (2019), Qiao et al. (2019) |
| | | | MCF-7/ADR | 8.17 µM (48 h) | – | – | |
| | | | MDA-MB-453 | 10.32 µM (48 h) | – | – | |
| <i>Anabas testudineus</i> | AtMP1 | 2378.53 Da | MDA-MB-231 | 9.35 µg/mL (48 h) | Bax, p53, caspase-3, caspase-9, Bcl-2 | Anti-bacteria | Najm et al. (2021) |
| | AtMP2 | 2088.35 Da | MCF-7 | 8.25 µg/mL (48 h) | – | – | |
| | | | MDA-MB-231 | 6.97 µg/mL (48 h) | Bax, p53, caspase-3, caspase-7, caspase-8, caspase-9, Bcl-2 | – | |
| | | | MCF-7 | 5.89 µg/mL (48 h) | – | – | |
| <i>Apis mellifera</i> | Melittin | 2840 Da | MCF-7 | 1.64 µM (24 h) | – | Anti-inflammation, anti-bacteria, anti-viruses, anti-parasites, anti-fungi, lytic effect, immune modulation, dermatological effects | Duffy et al. (2020), Memariani and Memariani (2020), El Mehdi et al. (2021), Guha et al. (2021) |
| | | | T-47D | 3.64 µM (24 h) | – | – | |
| | | | ZR-75-1 | 2.11 µM (24 h) | – | – | |
| | | | MDA-MB-231 | 1.14 µM (24 h) | – | – | |
| | | | SUM149 | 0.94 µM (24 h) | – | – | |
| | | | SUM159 | 1.94 µM (24 h) | – | – | |
| | | | MDA-MB-453 | 1.42 µM (24 h) | – | – | |
| | | | SKBR3 | 1.26 µM (24 h) | – | – | |
| <i>Bungarus fasciatus</i> | Phospholipase A ₂ | 13,082.91 Da | MCF-7 | ~7.63 µM (72 h) | – | – | Tran et al. (2019) |
| <i>Chinemys reevesii</i> | TP-1 | 1410.7 Da | MCF-7 | 2.7 mg/mL (24 h) | – | – | Shi et al. (2018) |

Table 1 (continued)

| Source | Name or type | Molecular weight | Cell models | Antiproliferation (IC ₅₀) | Potential target proteins | Other bioactivities | References |
|-----------------------------------|--------------------|--|--------------------------------|---|---------------------------|--|---|
| <i>Cuora trifasciata</i> | M2 | – | MCF-7 | 500 µg/mL (74.7%, 48 h) [†] | – | – | Mao et al. (2017) |
| | F4 | – | | 500 µg/mL (70.59%, 48 h) [†] | – | – | |
| <i>Drosophila virilis</i> | SK84 | 9 kDa | MCF-7 | 50 µM (72 h) | – | Anti-bacteria | Lu and Chen (2010) |
| <i>Glycydus ussuriensis</i> | Ussurin | 7.4 kDa | MDA-MB-231 | 6.1 µg/mL (48 h) | – | – | Sun (2013) |
| Milk and dairy products | α-lactalbumin | 14.2 kDa | MDA231-LM2 | 20 g/L (85.7%, 48 h) [†] | – | Anti-bacteria, anti-virus | Ng et al. (2015), Li et al. (2019a), Wang et al. (2019), Permyakov (2020) |
| | β-lactoglobulin | 18.4 kDa | | 20 g/L (83.4%, 48 h) [†] | – | Anti-bacteria, anti-virus | |
| | Lactoferrin | 80 kDa | | 20 g/L (78.3%, 48 h) [†] | – | Iron transfer, anti-bacterial, anti-virus, anti-fungi, anti-inflammation | |
| <i>Misgurnus anguillicaudatus</i> | LPH-IV | < 3 kDa | MCF-7 | 40 µg/mL (~95%) [†] | – | Anti-oxidation | (You et al. 2011) |
| <i>Pandanus imperator</i> | Pantinin-1 | 1545.90 Da | MDA-MB-231 | 28.5 µM (24 h) | – | Anti-bacteria | Zeng et al. (2013), Crusca et al. (2018) |
| | Pantinin-2 | 1403.71 Da | | 12.5 µM (24 h) | – | – | |
| | Pantinin-3 | 1490.80 Da | | 13.5 µM (24 h) | – | – | |
| <i>Rana chensinensis</i> | Temporin-1CEa | 1751.1 Da | MCF-7 | 31.91 µM (24 h); 34.50 µM (48 h) | – | Anti-bacteria | Shang et al. (2009), Wang et al. (2012) |
| Sea cucumbers | SCIP | <2000 Da (98.41%) <1041 Da (95.36%) | MDA-MB-231 Bcap-37 MCF-7 | 57.94 µM (24 h); 54.95 µM (48 h) 39.42 µM (24 h); 38.39 µM (48 h) – | – | – | Wei et al. (2021) |
| <i>Scyllorhinus canicula</i> | K092A | 1978 Da | ZR-75-1 | 1.22 mg/mL (96 h) | – | – | Bosseboeuf et al. (2019) |
| | | | MCF-7 | 1.09 mg/mL (96 h) | – | – | |
| <i>Thunnus tonggol</i> | PAB2 | 1206 Da | MCF-7 | 8.1 µM (72 h) | – | – | Hsu et al. (2011) |
| | PRB2 | 1124 Da | | 8.8 µM (72 h) | – | – | |
| | PAH _{2,5} | > 2.5 kDa | | 1.39 mg/mL (72 h) | – | – | Hung et al. (2014) |

Table 1 (continued)

| Source | Name or type | Molecular weight | Cell models | Antiproliferation (IC ₅₀) | Potential target proteins | Other bioactivities | References |
|------------------------------|----------------|--------------------------------|--------------------------|--|---------------------------|---|--|
| <i>Xenopus laevis</i> | XLAsp-P1 | 607.763 Da | MCF-7 | <5 µg/mL (24 h) ¶ | – | Anti-bacteria | Li et al. (2016a) |
| <i>Agaricus placomyces</i> | Laccase | 68 kDa | MCF-7 | 1.8 µM | – | Anti-HIV-1 | Sun et al. (2012) |
| <i>Agrocybe cylindracea</i> | Laccase | 58 kDa | MCF-7 | 6.5 µM (72 h) | – | Anti-HIV-1 | Hu et al. (2011) |
| <i>Bacillus megaterium</i> | Iturin A | – | MDA-MB-231 MCF-7 | 7.98 µM (48 h) 12.16 µM (48 h) | MD-2 | – | Dey et al. (2015, 2017) |
| <i>Boletus edulis</i> | BEL | 15,806 Da | MCF-7 | 10 µg/mL (77%) [†] | – | – | Bovi et al. (2011) |
| <i>Calvatia caelata</i> | CULP | 8 kDa | MDA-MB-231 | 100 nM (48 h) | – | Cell free translation-inhibition, ribonuclease, N-glycosidase, anti-mitosis | Lam et al. (2001) |
| <i>Cordyceps militaris</i> | Cordymin | 10,906 Da | MCF-7 | – | – | Anti-fungi, anti-HIV-1 | Wong et al. (2011) |
| | CMP | 12 kDa | MCF-7 | 9.3 µM (72 h) | – | Protease, anti-fungi | Park et al. (2009) |
| <i>Cyanobacterium</i> | Brintonamide C | 951.5311 [M + Na] ⁺ | MDA-MB-231 | 100 µM (48 h) | – | Kallikrein 7 inhibitor | Al-Awadhi et al. (2018) |
| | Brintonamide D | 909.4765 [M + Na] ⁺ | | | CCR10 | | |
| | Brintonamide E | 909.4773 [M + Na] ⁺ | | 14.9 µM (48 h) | | | |
| <i>Galaxaura filamentosa</i> | Galaxamide | 594.5 [M + H] ⁺ | MCF-7 | 10.25 µg/mL (48 h) | – | – | Xu et al. (2008), Lunagariya et al. (2017) |
| | Galaxamide 1 | 628.7 [M + H] ⁺ | MDA-MB-231 MCF-7 | 8.27 µg/mL (48 h) 4.76 µg/mL (48 h) | – | – | |
| | Galaxamide 2 | 678.8 [M + H] ⁺ | MDA-MB-231 MCF-7 | 5.83 µg/mL (48 h) 3.16 µg/mL (48 h) | – | – | |
| | Galaxamide 3 | 667.7 [M + H] ⁺ | MDA-MB-231 MCF-7 | 4.48 µg/mL (48 h) 1.72 µg/mL (48 h) | – | – | |
| <i>Ganoderma atrum</i> | FIP-gat | 12.45 kDa | MDA-MB-231 MDA-MB-231 | 3.51 µg/mL (48 h) 9.96 µg/mL (72 h) | – | – | Xu et al. (2016) |

Table 1 (continued)

| Source | Name or type | Molecular weight | Cell models | Antiproliferation (IC ₅₀) | Potential target proteins | Other bioactivities | References |
|----------------------------------|---------------|------------------|-------------|---------------------------------------|---------------------------|--|--|
| <i>Ganoderma lucidum</i> | FIP-glu | 13.1 kDa | MCF-7 | – | – | Immunomodulation, anti-allergy, hemagglutination | Li et al. (2011b, 2016b) |
| <i>Haliclona caerulea</i> | Halilectin-3 | 40 kDa (Trimer) | MCF-7 | 100 µg/mL | – | Hemagglutination | Carneiro et al. (2013), do Nascimento Neto et al. (2018) |
| <i>Hericium erinaceum</i> | HEA | 51 kDa | MCF-7 | 76.5 µM (48 h) | – | Anti-HIV-1, hemagglutination | Li et al. (2010b) |
| <i>Lignosus rhinocerotis</i> | FIP-Irh | 12.59 kDa | MCF-7 | 0.34 µM (24 h) | – | Hemagglutination | Pushparajah et al. (2016) |
| <i>Lignosus rhinocerus</i> | F5 | – | MCF-7 | 3.00 µg/mL (72 h) | – | – | Yap et al. (2018) |
| <i>Pholiota adiposa</i> | PAL | 16 kDa | MCF-7 | 3.2 µM (48 h) | – | Hemagglutination, anti-HIV-1 | Zhang et al. (2009) |
| <i>Pleurotus nebrodensis</i> | Neproteolysin | 27 kDa | Bre-04 | 50 µg/mL (98.4%, 48 h) [‡] | – | Anti-virus | Kong (2007) |
| <i>Russula delica</i> | Ribonuclease | 14 kDa | MCF-7 | 7.2 µM (48 h) | – | Ribonuclease | Zhao et al. (2010) |
| <i>Russula lepida</i> | RLL | 32 kDa | MCF-7 | 0.9 µM (48 h) | – | Hemagglutination | Zhang et al. (2010) |
| <i>Stachybotrys chartarum</i> | FIP-sch3 | 12.568 Da | MCF-7 | – | – | – | Li et al. (2016b) |
| <i>Streptomyces attratus</i> | Ilamycin C | – | MCF-7 | 15.93 µM (48 h) | – | Anti-tuberculosis | Ma et al. (2017), Xie et al. (2019) |
| | | | MDA-MB-231 | 7.26 µM (48 h) | | | |
| | | | BT-549 | 6.91 µM (48 h) | | | |
| | Ilamycin E | | HCC1806 | 47.50 µM (72 h) | – | | Ma et al. (2017), Zhou et al. (2019) |
| | | | HCC1937 | 14.24 µM (72 h) | | | |
| | | | MDA-MB-468 | 24.56 µM (72 h) | | | |
| | | | MDA-MB-231 | 33.72 µM (72 h) | | | |
| | | | T-47D | 18.95 µM (72 h) | | | |
| | | | MCF-7 | 40.27 µM (72 h) | | | |
| | | | SKBR3 | 26.18 µM (72 h) | | | |
| | | | BT-474 | 30.86 µM (72 h) | | | |
| <i>Streptomyces mangrovisoli</i> | CLP | – | MDA-MB-231 | 73.4 µM (48 h) | CD151 | Anti-bacteria, anti-oxidation | Ser et al. (2015), Ksgk et al. (2020) |
| | | | MDA-MB-468 | 67.4 µM (48 h) | | | |

IC₅₀, the mean inhibitory concentration; [‡] the inhibition ratio; [§] the median effect dose (EC₅₀); [¶] the median lethal concentration (LC₅₀)

ADR adriamycin; Bax Bcl-2-associated X protein; Bcl-2 B cell lymphoma 2; CCR10 chemokine receptor type 10; CD151, cluster of differentiation 151; MD-2, myeloid differentiation factor 2

Table 2 Anti-tumor activities of bioactive proteins/polypeptides in the animal models of breast cancer

| Source | Name | Dose | Tumor suppression rate | Animal model | References |
|----------------------------|-----------------|----------------------------|------------------------|----------------------------------|--------------------------------|
| <i>Amolops hainanensis</i> | HN-1 | 4 mg/kg | 64.4% (35 days) | 4T1 cells in BALB/c mice | Qiao et al. (2019) |
| | | | 65.44% (35 days) | MCF-7 cells in BALB/c mice | Qiao (2019) |
| <i>Apis mellifera</i> | Melittin | 5 mg/kg | – | T11 cells in BALB/c mice | Duffy et al. (2020) |
| <i>Bacillus megaterium</i> | Iturin A | 5 and 10 mg/kg | – | MDA-MB-231 cells in BALB/c mice | Dey et al. (2015) |
| Milk and dairy products | Lactoferrin | 10 ⁸ pfu/mL | 42.8% (14 days) | EMT6 cells in Kunming mice | Wang (2011), Li et al. (2019a) |
| | | 5 × 10 ⁸ pfu/mL | 52.64% (14 days) | | |
| | | 100 mg/kg | 55.42% (25 days) | | |
| | α-Lactalbumin | 100 mg/kg | 45.78% (25 days) | MDA231- LM2 cells in BALB/c mice | |
| | β-Lactoglobulin | 100 mg/kg | 44.18% (25 days) | | |
| <i>Pilose antler</i> | PAWPs | 20 mg/kg | 32.08% (28 days) | 4T1 cells in BALB/c mice | Zheng et al. (2020) |

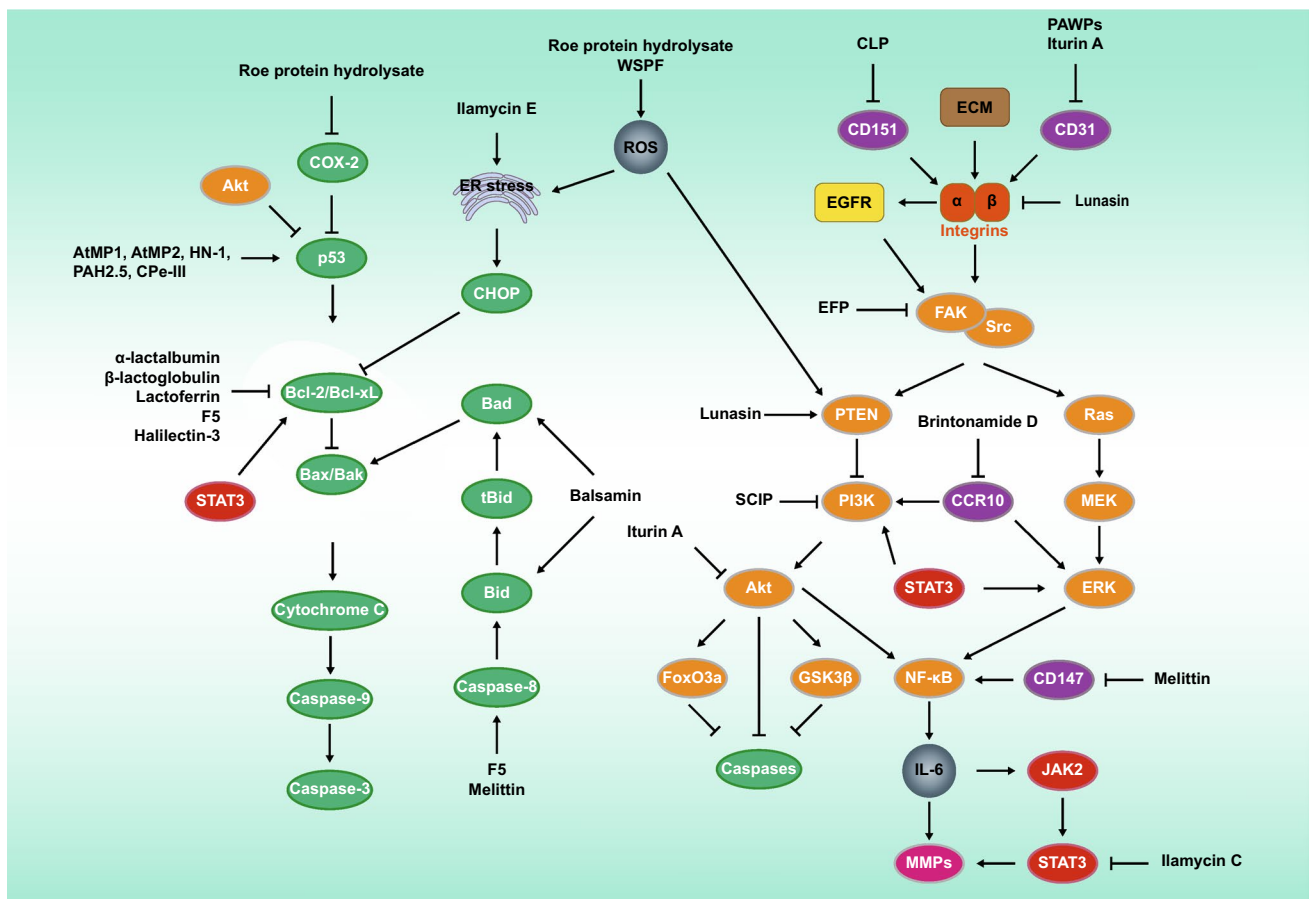


Fig. 1 Possible anti-tumor mechanisms of bioactive proteins/polypeptides against breast cancer. *Akt*, PKB protein kinase B; *Bad* Bcl-xL/Bcl-2-associated death promoter; *Bak* Bcl-2 antagonist killer 1; *Bax* Bcl-2-associated X protein; *Bcl-2* B cell lymphoma 2; *Bcl-xL* B-cell lymphoma extra-large; *Bid* BH3-interacting domain death agonist; *CCR10* chemokine receptor type 10; *CD147* cluster of differentiation 147; *CD151* cluster of differentiation 151; *CD31*, *PECAM-1* platelet endothelial cell adhesion molecule-1; *CHOP* C/EBP homologous protein; *COX-2* cyclooxygenase 2; *ECM* extracellular matrix; *EGFR* epidermal growth factor receptor; *ER* endoplasmic reticulum; *ERK*

extracellular signal-regulated kinases; *FAK* focal adhesion kinase; *FoxO3a* forkhead box O3a; *GSK3β* glycogen synthase kinase 3-β; *IL-6* interleukin 6; *JAK2* Janus protein tyrosine kinase 2; *MAPK* mitogen-activated protein kinase; *MEK* mitogen-activated protein kinase kinase; *MMPs* matrix metalloproteinases; *PI3K* phosphatidylinositol 3-kinase; *PTEN* phosphatase and tensin homolog; *Ras* rat sarcoma virus; *ROS* reactive oxygen species; *Src* proto-oncogene tyrosine-protein kinase Src; *STAT3* signal transducer and activator of transcription 3; *tBid* truncated Bid

reduces CD151 expression (Kgc et al., 2020). Melittin is the main component of bee venom (Raghuraman and Chattopadhyay, 2007), and inhibits the activation of FAK and MMP-9 by blocking the PI3K/Akt/mammalian target of rapamycin (mTOR) signaling pathway (Jeong et al., 2014). Melittin consists of 26 amino acids (GIGAVLKVLTTGLPALISWIKRKRQQ) with a hydrophobic N-terminal and a hydrophilic C-terminal (Raghuraman and Chattopadhyay, 2007). Melittin with the total +6 charges at physiological pH binds to negatively charged membrane surface and then disturbs the membrane integrity, ultimately leading to cell lysis (Jamasbi et al., 2016), and is also considered as a promising candidate for cancer chemotherapy (Schweizer, 2009). Lunasin, a 43-amino acid peptide isolated from soybean seed (Galvez and de Lumen, 1999), is divided into four regions: N-terminus, central part, RGD motif and C-terminus (Jones and Srivastava, 2014). The full sequence of lunasin exerts cytotoxicity to MDA-MB-231 cells through inhibition of H3 and H4 acetylation (Hernandez-Ledesma et al., 2011), while the RGD motif involves in cancer metastasis (Niebler et al., 2017). It can also inhibit the phosphorylation of FAK, Src, Akt, and ERK, suppress the nucleus translocation of NF- κ B, and reduce the activity and expression of MMP-2 and -9, resulting in the inhibition of invasion of MCF-7 and MDA-MB-231 cells (Jiang et al., 2016). This mechanism might involve that lunasin interacts with integrins, leading to the suppression of the signaling axis (Vuyyuri et al., 2018). Besides, an earthworm fibrinolytic protein (EFP) isolated from *Eisenia fetida* inhibits FAK expression and the migration of MCF-7 cells (Chen, 2014).

A glycoprotein cluster of differentiation 147 (CD147) is an MMP inducer and as well as promotes interleukin (IL)-6 production via NF- κ B (Dana et al., 2021). IL-6 primarily activates Janus protein tyrosine kinase (JAK) 1 and JAK2 to drive signal transduction, including the activity of signal transducer and activator of transcription (STAT), mitogen-activated protein kinase (MAPK), and PI3K-Akt (Kang et al., 2020). The activated STAT3 increases the expression of MMP-2, -7, and -9 (Banerjee and Resat, 2016; Cao et al., 2022). Melittin downregulates CD147 and MMP-9, leading to inhibiting MCF-7 cell invasion (Wang et al., 2017). Ilamycins are a series of cyclic peptides and are isolated from the deep South China Sea-derived *S. atratus* SCSIO ZH16 and engineered mutant strains (Ma et al., 2017). Ilamycin C can inhibit the invasion and migration of MDA-MB-231 cells via decreasing MMP-2 and MMP-9 by suppressing IL-6-induced STAT3 phosphorylation (Xie et al., 2019).

Chemokine receptor type 10 (CCR10) is a member of the chemokine receptor subfamily and promotes cancer cell invasion and migration through the ERK and PI3K/Akt signaling pathway with the regulation of MMPs (Lin et al., 2017; Liu et al., 2021). A modified linear peptide brintonamide D from samples of intertidal cyanobacterial mats can be used

as a CCR10 antagonist to reduce the proliferation and migration of MDA-MB-231 cells (Al-Awadhi et al., 2018). Brintonamide D forms hydrogen bonds with Arg247, Arg322 and Arg345 of CCR10 and the aromatic ring on the modified side of brintonamide D has π - π interaction with residue Tyr227 in the middle of the CCR10 β -sheet.

Inducing apoptosis

Apoptosis is a kind of regulated cell death process (Carneiro and El-Deiry, 2020). Cancer cells are capable of evading apoptosis (Brown and Attardi, 2005). Reactive oxygen species (ROS) increase the levels of phosphatase and tensin homolog (PTEN), as a tumor suppressor gene, negatively regulating PI3K/Akt pathway (Wang et al., 2020, 2022), thereby inducing caspases-dependent apoptosis through itself, forkhead box O3a (FoxO3a) (Yan et al., 2020), and glycogen synthase kinase 3- β (GSK3 β) (Guo et al., 2020). Members of the caspase family participate in the initiation and execution of apoptosis (Boice and Bouchier-Hayes, 2020). In MCF-7 and MDA-MB-231 cells, roe protein hydrolysate prepared from defatted *Alburnus tarichi* roe powder causes the significant production of intracellular ROS, and significantly increases the expressions of caspase-3, -7, -8, and -9, inducing apoptosis (Berkoz et al., 2020). In MDA-MB-231 cells, lunasin does not exhibit the effect of apoptosis, but it promoted aspirin-induced apoptosis (Hsieh et al., 2010). While, in MCF-7 cells, lunasin upregulates PTEN promoter activity, increases PTEN transcript and protein levels, and enhances nuclear PTEN localization, leading to cellular apoptosis (Pabona et al., 2013). A small molecular oligopeptide, sea cucumber intestinal peptide (SCIP) with being rich in hydrophobic amino acids (Ala, Val, Leu, Gly, Phe, and Met) and branched-chain amino acids (Val, Ile, and Leu), is extracted from sea cucumber intestines and promotes the apoptosis of MCF-7 cells through the inactivation of PI3K/Akt signaling pathway with elevating the expression of cleaved caspase-9 and -3 (Wei et al., 2021). But the detailed mechanism remains unclear. In MDA-MB-231 and MCF-7 cells, the apoptotic effect of iturin A is attributed to the Akt-mediated FoxO3a and GSK3 β (Dey et al., 2015). Although the activation of caspases is a feature of apoptosis, HN-1, a naturally occurring host defense peptide identified from *Amolops hainanensis*, induces caspase-independent apoptosis (Qiao et al., 2019).

Cyclooxygenase 2 (COX-2) is an inducible enzyme compared with constitutive COX-1 and is often overexpressed in breast cancer with poor survival (Ristimaki et al., 2002). COX-2 binds with and inactivates p53 (Feng et al., 2019), which regulates apoptotic genes directly and indirectly (Mihara et al., 2003; Hemann and Lowe, 2006). B cell lymphoma 2 (Bcl-2) gene family, including

pro-apoptotic members such as Bcl-2-associated X protein (Bax), Bcl-2 antagonist killer 1 (Bak), Bcl-2-related ovarian killer (Bok), Bcl-2-interacting mediator of cell death (Bim), BH3-interacting domain death agonist (Bid), B-cell lymphoma extra-large (Bcl-xL)/Bcl-2-associated death promoter (Bad), and p53 upregulated modulator of apoptosis (Puma), and anti-apoptotic members such as Bcl-2, Bcl-xL, Bcl-2-like protein 2 (Bcl-w), and mantle cell lymphoma 1 (Mcl-1), has a significant role in regulating apoptosis (Ashkenazi et al., 2017). The activation of caspases is mainly regulated by the Bcl-2 family (Tzifi et al., 2012). It has been found that in MCF-7 cells, the roe protein hydrolysate downregulates COX-2 level (Berkoz et al., 2020). In MCF-7 and MDA-MB-231 cells, tuna cooking juice hydrolysate by protease XXIII (PA) with > 2.5 kDa ultrafiltration fraction (PAH_{2.5}) (Hung et al., 2014), CPe-III derived from chickpea albumin hydrolysate (Xue et al., 2015), and AtMP1 and AtMP2 identified from *Anabas testudineus* antimicrobial peptides (Najm et al., 2021) significantly increase the expressions of p53 and Bax, decrease the level of Bcl-2 which could be overwhelmed by Bax (Yin et al., 1997), and upregulate caspases levels. HN-1 also activates p53 and induces a p53-dependent increase of Bax/Bcl-2 ratio in xenograft tumors (Qiao et al., 2019). Molecular docking analysis showed that Arg1, Gln2, Ala6, Ala8, and Gln9 of CPe-III combine the DNA binding domain of p53 protein (Thr102, Leu111, Asn131, Gln144, Asp228, and Asn268) by hydrogen bonds, resulting in the induction of p53 expression (Xue et al., 2015). Najm et al. found that hydrogen bonds formed between AtMP1/AtMP2 and p53, Bax, Bcl-2, or caspases (Najm et al., 2021). Balsamin is a type I ribosome-inactivating protein purified from *Momordica balsamina* (Kaur et al., 2012). It increases the expressions of Bax, Bid, and Bad, reduces the levels of Bcl-2 and Bcl-xL, and increases the activities of caspase-3 and -8 in MCF-7 and BT549 cells (Ajji et al., 2017). Halilectin-3 containing three subunits is isolated from *Haliclona caerulea* (Carneiro et al., 2013), and induces MCF-7 apoptosis with a decrease of Bcl-2 and an increase of caspase-9 (do Nascimento-Neto et al., 2018). Both the α -chain and β -chain of halilectin-3 have *N*-glycosylation sites with affinity to *N*-acetylgalactosamine (GalNAc) (Carneiro et al., 2013), thereby recognizing abnormal expressing GalNAc-containing antigen on MCF-7 cells (do Nascimento-Neto et al., 2018). α -Lactalbumin, β -lactoglobulin, and lactoferrin, nutritional components in milk and dairy products, downregulate Bcl-2 and upregulate Bax, leading to increasing caspase-3 in MDA-LM2 cells (Li et al., 2019a). Melittin increases the levels of Bax, caspase-3, and -8 in MDA-MB-231 cells (Daniluk et al., 2019; Mir Hassani et al., 2021). A cytotoxic protein fraction F5 is isolated and is mainly composed of 97.29% serine protease encoded by GME4347_g (Yap et al., 2018).

The F5 induces the increases of Bax, Bid, and cleaved Bid, and the decrease of Bcl-2, leading to the upregulation of caspase-8 and -9 activities.

C/EBP homologous protein (CHOP) is a pro-apoptotic endoplasmic reticulum (ER) stress marker, which can be regulated by ROS-mediated ER stress (Zhu et al., 2022), subsequently regulating Bcl-2/Bax (Li et al., 2019c; Liu et al., 2020). WSPF is a novel protein fraction isolated from *Withania somnifera* roots and induces apoptosis of MDA-MB-231 cells through the production of extensive ROS, leading to reducing Bcl-2 expression, increasing Bax expression, and elevating cleaved caspase-3 expression (Dar et al., 2019). Ilamycin E is another cyclic peptide (Ma et al., 2017). It activates ER stress, increases CHOP, and downregulates Bcl-2, which promotes apoptosis in HCC1937 and MDA-MB-468 cells (Zhou et al., 2019).

Bcl-2 can also be regulated by STAT3 (Liu et al., 2017b). Ilamycin C promotes Bax/Bcl-2-related caspase-dependent apoptosis through IL-6/JAK2/STAT3 as well (Xie et al., 2019).

Cell cycle arrest

The cell cycle is a tightly regulated process including Gap 1 (G1), DNA-synthesis (S), Gap 2 (G2), and mitosis (M) phases. The core cell-cycle proteins are frequently dysregulated in human cancers, and targeting these proteins seems to represent an effective strategy for inhibiting tumors (Suski et al., 2021). Mitogenic signals upregulate cyclin D, which binds and activate cyclin-dependent kinase (CDK) 4 or CDK6 to drive the progression from the G0 or G1 into the S phase. Degradation of cyclin D is a promising targeted therapy for the cancer cell cycle (Caudron-Herger and Diederichs, 2021; Chaikovskiy et al., 2021; Maiani et al., 2021; Simoneschi et al., 2021). p21 and p27 are capable of inhibiting cyclin/CDK complexes comprising CDK1 or 2 and cyclin A; CDK1 and CDK2 can be activated by cyclin A which has a critical role in the S and G2-M phase (Suski et al., 2021; Garcia-Osta et al., 2022). Ilamycin E decreases Cyclin D1, and increases p21 and p27 levels, thereby inducing G1/S cell cycle arrest in HCC1937 and MDA-MB-468 cells (Zhou et al., 2019). PAH_{2.5} increases p21 and p27 protein expression and decreases cyclin A expression, which induces cell cycle arrest in the S phase in MCF-7 cells (Hung et al., 2014).

Conclusions and perspectives

Breast cancer is the leading cause of cancer death among women (Ghoncheh et al., 2016). It is a hormone-dependent tumor (Russnes et al., 2017), and its targeted therapies

include human epidermal growth factor receptor 2-targeted agents and endocrine therapy (Turashvili and Brogi, 2017). However, drug resistance is still a major challenge in the treatment of breast cancer (Karami Fath et al., 2022). Bioactive proteins/polypeptides exhibit a great potential against cancers, including breast cancer. Identification of novel bioactive proteins/polypeptides and development of novel functions of the existing bioactive proteins/polypeptides are necessary. Generally, protein is digested and absorbed in the form of amino acids from diet, although proteins with medicinal value still have bioactivity (Lee et al., 2018). Treatments of iturins (Zhao et al., 2018), FIP-gmi (Hsin et al., 2020) and PAWPs (Zheng et al., 2020) by gavage still exhibit bioactivity without side effects. On the other hand, unfortunately, some proteins/polypeptides such as melittin exhibits extensive hemolysis and cytotoxicity, which may limit its application in clinical practice (Askari et al., 2021). Thus, the pharmacokinetics and pharmacodynamics of bioactive proteins/polypeptides have been well studied further. At the same time, it is critical to modify the proteins/polypeptides to enhance their effects (Berdan et al., 2021). Several analogues of galaxamide which is isolated from *Galaxaura filamentosa* are synthesized (Xu et al., 2008; Lunagariya et al., 2017). These analogues exhibit greater excellent toxicity toward breast cancer cells. Whey protein

isolates modified with rosmarinic acid at alkaline conditions exhibits enhanced antioxidative capacity (Ali et al., 2018). The covalent complex of soy protein isolates and epigallocatechin gallate has higher thermal stability and oxidation resistance and a polyphenol-protective effect (Zhou et al., 2020a). A peptide drug conjugate named TAMpepK, consisting of melittin and a pro-apoptotic peptide, targets M2-like tumor-associated macrophages, thereby inhibiting breast cancer metastasis in the mouse model (Lee et al., 2022). In the previous study, we found that *N*-glycosylation significantly improves the functional properties of FIP-glu (Li et al., 2021a). Besides, combination regimen-based therapies are promising strategies (Li et al., 2021b). For example, Co-treatment of melittin and hormone therapeutic drugs (Yen et al., 2022), drugs with anti-tumor potential (Duarte et al., 2022), agents (Shaw et al., 2019), and miRNAs (Motiei et al., 2021) reveals synergistic effects in breast cancer cells. Bioactive proteins/polypeptides are suitable for gene therapy, a promising strategy for cancer treatment (Zhou et al., 2020b). The anti-tumor research of bioactive proteins/polypeptides is mainly performed in cell and animal models. However, relevant clinical studies are rare (Table 3). Although the anti-tumor mechanisms of bioactive proteins/polypeptides have been actively studied, there are still problems in the production, administration and regulation of

Table 3 Clinical research of bioactive proteins/polypeptides

| Proteins/Polypeptides | Population | Treatment | Diseases | References |
|------------------------|---|---|--|-------------------------------|
| α -lactalbumin | 14 poly-cystic ovary syndrome women | 50 mg twice a day for 6 months | Poly-cystic ovary syndrome | Hernandez Marin et al. (2021) |
| | 20 poly-cystic ovary syndrome women | | | |
| | 18 healthy volunteers | 150 mg (after fasting for 12 h) | Myo-inositol intestinal absorption | Monastra et al. (2018) |
| | 120 women with gestational diabetes mellitus | 50 mg twice a day for 2 months | Gestational diabetes mellitus | D'Anna et al. (2021) |
| β -lactoglobulin | 9 healthy males | 0.6 g/kg during the study day | Muscle protein kinetics and metabolism | Mose et al. (2021) |
| | 16 type 2 diabetes mellitus patients | 25 g (30 min before breakfast and dinner) | Type 2 diabetes mellitus | Smedegaard et al. (2021) |
| Lactoferrin | 743 very low birth weight neonates | 100 mg/day for 30 days | Necrotizing enterocolitis | Manzoni et al. (2014) |
| | 472 very low birth weight neonates | | Sepsis | Manzoni et al. (2009) |
| | 190 birth weight < 2500 g | 200 mg/kg/day for 4 weeks | | Ochoa et al. (2015) |
| | 555 children (12~18 months old) | 0.5 g twice a day for 6 months | Diarrhea in children | Ochoa et al. (2013) |
| | 472 very low birth weight neonates | 100 mg/day for 6 weeks | Invasive fungal infections | Alfaleh (2012) |
| | 48 adult women | – | Bacterial vaginosis | Russo et al. (2019) |
| Lunasin | 31 individuals with mild to moderate cardiometabolic risk factors | 0.6 mg/kg/day for 8 weeks | Cardiometabolic risk factors | Haddad Tabrizi et al. (2020) |

bioactive proteins/polypeptides (Chakrabarti et al., 2018). Therefore, further studies are needed to evaluate the physiological efficacy of these bioactive proteins/polypeptides in human clinical studies. To summarize, bioactive proteins/polypeptides have impressive anti-tumor effects against breast cancer. It is suggested that bioactive proteins/polypeptides with great potential are promising agents for the treatment of breast cancer.

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Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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