Trametes genus, a source of chemical compounds with anticancer activity in human osteosarcoma: A systematic review

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ABSTRACT
Natural bioactive compounds have aroused great interest for their potential benefits in human health, particularly in the prevention and treatment of cancer. The aim of this systematic review is to inspect whether bioactive compounds present in mushrooms of the genus Trametes have shown anticancer activity in human osteosarcoma. According to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) parameters, this review was carried out using Science Direct, PubMed Central, and Embase as electronic databases to select the articles that evaluated the cytotoxic effects of extracts or compounds isolated from mushrooms of the genus Trametes in human osteosarcoma. A total of 15 studies out of 165 met the inclusion criteria and are included in our systematic review. Among them, six studies evaluated extracts, eight evaluated polysaccharides, and one evaluated tetralin lignans of different species of the genus Trametes. Although only two research articles evaluated the effects of chemical compounds such as polysaccharides on human osteosarcoma, all of them have confirmed the potential of compounds present in mushrooms to treat different types of cancer.

INTRODUCTION
The most common primary bone cancer in children and teenagers is osteosarcoma (Chen et al., 2018a; Suárez et al., 2017). The main difficulty in treating this cancer is that it begins to develop in the skeletal system and it can develop metastasis and spread to other organs of the body, making its timely diagnosis complex. The standard osteosarcoma treatment includes local surgical control, with radical surgery or limb preservation, and the administration of polychemotherapy (methotrexate, doxorubicin, cisplatin, and ifosfamide) (Suárez et al., 2017). The prognosis of patients with osteosarcoma can be improved with the combination of surgery and chemotherapy. However, a considerable number of patients have developed resistance to chemotherapy (Chen et al., 2018b). In addition, some chemotherapeutic agents are not selective since they also attack normal cells and generate toxic side effects (Ferrari and Palmerini, 2007; Zhao et al., 2015b). To overcome this situation, antitumor agents or chemical products with increased efficiency and reduced toxicity are being developed (Zhao et al., 2015b).

For the treatment of cancer, Chinese medicines have been used as either food ingredients or supplements. Generally, cancer patients use herbal medicines with conventional medical treatment to improve the desired results (Ko et al., 2017). Among these Chinese herbal medicines, mushrooms represent a source of compounds with antioxidant, immunomodulating, anti-inflammatory, antimicrobial, and anticancer properties (Ricciardi et al., 2017). Mushrooms have been consumed for many years because they have a large number of bioactive compounds, including polysaccharides, proteins, and lipids (Wasser, 2011). Specifically, the anticancer potential to treat various types of cancer by some species of the genus Trametes, such as Trametes versicolor (synonym Coriolus versicolor), Trametes gibbosa, Trametes hirsuta, Trametes lactinea, and Trametes robiniophila, has been reported. In general, this anticancer activity has been attributed to chemical compounds such as polysaccharides (He et al., 2018; Ricciardi et al., 2017; Rosendahl et al., 2012; Scarpari et al., 2017; Wang et al., 2017a, 2017b; Zhao et al., 2015a, 2015b) and tetralin lignans (Puri et al., 2006). Mushroom polysaccharides are significant compounds with anticancer, anti-oxidative, antidiabetic, antimicrobial, anti-inflammatory, and immunomodulatory activity. β-glucan is the main polysaccharide found in mushrooms and it makes up about half the mass of its cell wall (Amirullah et al., 2018).
T. versicolor essentially contains polysaccharide-K or Krestin (PSK) and polysaccharide peptide (PSP). In PSK, roughly 62% of the molecule is polysaccharide and 38% is protein and PSP is a protein-bound polysaccharide (Fritz et al., 2015). PSK has shown anticancer activity in breast, colorectal, and gastrointestinal cancers (Blagodatski et al., 2018; Kiyama, 2017). T. robianiphila has demonstrated an antiproliferative effect on the diversity of tumor cells via inducing apoptosis (Ren et al., 2009; Zhao et al., 2015a). Proteoglycans have been recognized as the principal components answerable for the anticancer activity of T. robianiphila (Li et al., 2015; Sun et al., 2013; Zhao et al., 2015b).

In this regard, the aim of this systematic review is to analyze the information from reports which demonstrate the anticancer activity of the bioactive compounds isolated from several species of the genus Trametes on human osteosarcoma.

MATERIALS AND METHODS

Search terms

The present systematic review involved research articles from the Science Direct, Pubmed Central and Embase databases from 2000 to May 2019. The search terms were “T. versicolor”, “osteosarcoma OR bone cancer OR anticancer”, and “bioactive compounds OR metabolites” and the keywords “in vivo OR in vitro” were used as a search strategy. The articles were selected first by the title, then by the summary, and finally by reading the full text. Two relevant articles were found through manual searches in the reference lists.

Inclusion and exclusion criteria

Finally, the articles were chosen by taking into account some inclusion and exclusion criteria (see Table 1).

Quality evaluation

The quality of the articles included in this review was systematically evaluated. The quality score was assigned considering the following five items: characterization of extracts or compounds of interest (2 points), anticancer tests in vitro, ex vivo, and in vivo (2 points for each test), and the use of controls in anticancer tests (2 points) for a maximum score of 10 points.

Quality evaluation of the parameters

Characterization of extracts or compounds of interest

- If the extract or the compound of interest is not characterized: 0 points.
- If the extract or the compound of interest is characterized by generic tests (presence of carbohydrates, total phenolic content, etc.): 1 point.

- If the extract or the compound of interest is characterized by specific tests (FTIR (Fourier-transform infrared spectroscopy), NMR (Nuclear Magnetic Resonance), etc.): 2 points.

Anticancer tests in vitro

- If in vitro anticancer tests are not performed: 0 points.
- If in vitro anticancer tests are performed: 2 points.

Anticancer tests ex vivo

- If ex vivo anticancer tests are not performed: 0 points.
- If ex vivo anticancer tests are carried out: 2 points.

Anticancer tests in vivo

- If in vivo anticancer tests are not performed: 0 points.
- If in vivo anticancer tests are performed: 2 points.

Use of controls in anticancer tests

- If controls are not used in anticancer tests: 0 points.
- If at least one control is used in anticancer tests (positive control or negative control): 1 point.
- If two controls are used in anticancer tests (positive control and negative control): 2 points.

Quality ranges

The articles with 8–10, 4–7, and 0–3 points were recognized as high, moderate, and low quality, respectively.

Data extraction

The information extracted from each study included author name, publication year, country, main objective, and main findings of each research. In order to guarantee the success of the revision process, the data analysis and assessment were carried out by three independent reviewers, who assessed the reproducibility and the probability of bias in each stage of the review.

RESULTS

Selection of studies

The initial search through databases identified 343 articles. After removing duplicates, the remaining 165 articles were reviewed based on the title and the abstract by reviewers. A total of 21 articles were reviewed based on full-text availability. Finally, the 15 studies included in our systematic review met the inclusion criteria. Figure 1 shows the flow diagram of the search results.

| Parameter                  | Inclusion criteria                  | Exclusion criteria                  |
|----------------------------|-------------------------------------|-------------------------------------|
| Language                   | English                             | Any other language                  |
| Type of publication        | Research articles                   | Review articles, editorial material, meeting summaries, letters, publications, and book chapters |
| Characterization           | Characterization of extracts or compound of interest | Uncharacterized extracts |
| Type of study              | In vitro and/or in vivo             | Any other type of study             |
| Genus of mushroom          | Any species of the Trametes genus   | Genus other than Trametes           |
Characteristics of the studies

Among the 15 research articles included, 2 studies evaluated the anticancer activity of ethanol extracts of the fruiting body (Janjušević et al., 2018) and basidiocarp and mycelium (Knežević et al., 2018); 4 studies evaluated the activity of a polysaccharide-rich aqueous extract of the fruiting body (Roca-Lema et al., 2019), an aqueous extract of the fruiting body (Ko et al., 2017; Luo et al., 2014), and mycelial biomass (Shnyreva et al., 2018). Moreover, 9 studies evaluated the activity of compounds such as polysaccharides (He et al., 2018; Zhao et al., 2015a, 2015b), PSK (Rosendahl et al., 2012), intracellular protein-polysaccharide (Wang et al., 2017a),
extracellular polysaccharide (Wang et al., 2017b), Tramesan (Ricciardi et al., 2017; Scarpari et al., 2017), and tetralin lignans (Puri et al., 2006). Table 2 describes some features of each study, involving the year of publication, country, objective, extract or compound of interest, and the species of the mushrooms used.

Results of individual studies

All studies evaluate the cytotoxic effects of extracts or derivate compounds from different species of the genus *Trametes* in cell lines of various types of cancer. In some of these research articles, the mechanism underlying these effects was identified. Table 3 shows the anticancer assays and the principal findings of the individual reports.

### Evaluation of the quality of the studies

Table 4 shows the quality assessment for each study based on the inclusion and exclusion criteria. The total average score was 4.8 ± 1.0. Hence, for articles where extracts were evaluated,
| Reference                          | Methods                                                                 | Anticancer tests                                                                 | Main findings                                                                                                                                                                                                 |
|----------------------------------|-------------------------------------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Roca-Lema et al., 2019           | In vitro: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay<sup>a</sup> | Negative control                                                               | Polysaccharide-rich extracts from *T. versicolor* and *G. frondosa* showed cytotoxic effects in LoVo and HT-29 human colon cancer cells. Moreover, these extracts inhibited oncogenetic potential, cell migration, and invasion in colon cancer cells. The combination of polysaccharide-rich extracts with 5-Fu increased cell cytotoxicity. |
| He et al., 2018                   | In vitro: MTT assay<sup>a</sup> and lactic dehydrogenase (LDH) assay<sup>b</sup> | Negative control                                                               | The *T. lactinea* polysaccharide fraction with the average molecular weight of 443.19 KDa (TLP-1) showed anticancer activity in HepG-2 cells, which was associated with a decrease in cell proliferation and an increase in LDH leakage and apoptotic cell population. Additionally, TLP-1 presented antioxidant activity. |
| Janjašević et al., 2018          | In vitro: MTT assay<sup>a</sup>                                         | Negative control                                                               | The ethanol extracts of fruiting bodies from *T. versicolor* exhibited cytotoxicity in MCF-7 and HepG2 tumor cell lines. This cytotoxicity may be due to the presence of gentisic, syringic, and protocatechuic acids. |
| Knežević et al., 2018            | In vitro: MTT assay<sup>a</sup>                                         | Negative control                                                               | The mycelium extracts from *T. gibbosa*, *T. hirtata*, and *T. versicolor* showed stronger cytotoxic effects than the basidiocarp extracts in cell lines of human cervical adenocarcinoma (HeLa), human colon carcinoma (LS174), and human lung adenocarcinoma (A549). These results can be related to a synergistic action of triterpenes, sugars, and polyphenols. Furthermore, the basidiocarps and mycelia extracts of these *Trametes* species inhibited the activity of acetylcholinesterase and tyrosinase. |
| Shnyreva et al., 2018            | In vitro: MTT assay<sup>a</sup>                                         | Unspecified control                                                             | The methylol-chloroform (1:1) extract of mycelial biomass from *T. versicolor* (strain It-1) inhibited the growth of lung, breast, cervix, and colon solid tumors. Also, the hot water extracts of mycelial biomass from *T. versicolor*, *Coprophora puteana*, and *Fomes fomentarius* showed antiproliferative effect on leukemia cell lines (Jurkat, K562, and THP-1). |
| Ko et al., 2017                   | In vitro: the bioluminescence measurements according to the average radiance | Negative control                                                               | The combination of *C. versicolor* aqueous extract and mZOL inhibited cell proliferation and osteogenesis on breast cancer cells MDA-MB-231-TXSA. This combination decreased tumor growth and preserved bone integrity in an intratibial breast tumor model. |
| Ricciardi et al., 2017           | In vitro: trypan blue dye exclusion assay<sup>a</sup>                   | Negative control                                                               | Tramesan inhibited the growth of human myeloid (OCI-AML3) and lymphoid (Jurkat) cell lines. Besides, the antiproliferative effect of Tramesan on AML cell lines was determined to be related to the induction of apoptosis. |
| Scarpari et al., 2017            | In vitro: counting the number of viable cells with light microscopy      | Negative control                                                               | Tramesan showed acytotoxic effect on murine cell lines of melanoma (B16-F10). Moreover, this compound can act as a proantioxidant molecule in different organisms. |
| Wang et al., 2017a                | In vitro: MTT assay<sup>a</sup>                                         | Negative control                                                               | The production of intracellular protein-polysaccharide (IPS) from *T. versicolor* was stimulated and improved in the presence of tyrosol. Besides, an increase in the total carbohydrate, protein, and glucose contents of IPS was observed, which was related to its strong antitumor activity. The antitumor activity of IPS was identified to occur through cell cycle arrest and an increase in apoptosis. |
| Wang et al., 2017b                | In vitro: MTT assay<sup>a</sup>                                         | Negative control                                                               | The production of extracellular polysaccharide (EPS) from *T. versicolor* was stimulated in the presence of farnesol. Farnesol altered the physicochemical properties of EPS. Furthermore, under farnesol stimulation, it was observed that EPS had more carbohydrate and uronic acid contents, and it also exhibited enhanced antioxidant and antitumor activities. |
| Zhao et al., 2015a                | In vitro: MTT assay<sup>a</sup>                                         | Negative control                                                               | *T. robiniophila* polysaccharide inhibited the proliferation of human osteosarcoma cell lines (OS U-2) through a mitochondria-dependent apoptotic pathway. This mechanism was related to an increase in the Bax/Bcl-2 ratio, loss of mitochondrial membrane potential (∆Ψm), release of cytochrome c, activation of caspase-9 and caspase-3, cleavage of PARP, and inhibition of MTDH expression. |
| Zhao et al., 2015b                | In vivo: measurement of tumor weight and tumor volume at the end of the experiment | Negative control                                                               | *T. robiniophila* polysaccharide was orally administered to nude mice with xenografted U-2 OS osteosarcoma tumors. The mechanism of suppression of tumor growth in mice occurred via a mitochondria-dependent apoptotic pathway, which was related to increased Bax/Bcl-2 ratio, activation of caspase-9 and caspase-3, repression of MTDH, and the cleavage of P ARP. |
| Luo et al., 2014                  | In vitro: MTT assay<sup>a</sup>                                         | Negative control                                                               | The aqueous extract of *C. versicolor* showed an antitumor and antimetastatic effect, and a bone protective effect against osteolysis induced by breast cancer. These results were supported by *in vitro* 4T1 cell migration and invasion inhibition and *in vivo* tumor weight and reducing lung metastasis in mice with 4T1 orthotopic tumors. |

Continued
the compounds like polysaccharides that presented a wide variety of mechanisms of anticancer activity. Among these mechanisms are the depolarization of the mitochondrial membrane, the cell cycle arrest, the nitric oxide pathway, and the immunomodulation (Khan et al., 2019).

The proteins implicated in proliferative pathways may induce or stop the apoptosis process in cells, thus allowing manipulation of the cell cycle. Apoptosis or programmed cell death occurs mostly through the caspase cascade (Pucci et al., 2003). On the other hand, depolarization of the mitochondrial membrane produces the release of cytochrome c into the cytoplasm. This release leads to the formation of an apoptosome complex, which produces the activation of caspases (caspase-9 and caspase-3), a group of cysteine proteases, which initiate apoptosis (Tian et al., 2016). Furthermore, an increase in the ratio of Bax/Bcl2 (apoptosis inducer/apoptosis suppressor) is related to apoptosis induction (Khan et al., 2019).

Several polysaccharides boost macrophages to produce NO (Nitric oxide) by positively regulating the inducible NO synthase activity. NO can induce cytotoxicity by inhibiting essential enzymes, depleting antioxidant stores, inducing lipids, and activating the cell cycle manipulation. Apoptosis or programmed cell death occurs mostly through the caspase cascade (Pucci et al., 2003). On the other hand, depolarization of the mitochondrial membrane produces the release of cytochrome c into the cytoplasm. This release leads to the formation of an apoptosome complex, which produces the activation of caspases (caspase-9 and caspase-3), a group of cysteine proteases, which initiate apoptosis (Tian et al., 2016). Furthermore, a decrease in the ratio of Bax/Bcl2 (apoptosis inducer/apoptosis suppressor) is related to apoptosis induction (Khan et al., 2019).

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peroxidation, and causing DNA damage. Also, most of these polysaccharides function independently to give anticancer activity, generating the release of cytokines and improving the expression of lymphocyte. It has also been indicated that the intensification in NO production generates the death of tumor cells via the caspase pathway. Furthermore, the polysaccharides have immunostimulant activity (Bao et al., 2013; Jiang et al., 2014; Khan et al., 2019).

Explanation of the results

Complete research articles incorporated in this systematic review indicated that extracts, as well as isolated compounds from different species of Trametes, displayed cytotoxic potential in various types of cancer. The ethanol extract obtained from fruiting bodies from T. versicolor blocked the proliferation in vitro of human breast adenocarcinoma (MCF-7) and human hepatocellular carcinoma (HepG2) cell lines (Janušević et al., 2018). Similarly, the ethanol extracts of basidiocarp and mycelium from T. gibbosa, T. hirsuta, and T. versicolor revealed in vitro cytotoxic activity against human cervix adenocarcinoma (HeLa), human colon carcinoma (LS174), and human lung adenocarcinoma (A549) cell lines (Knežević et al., 2018). Results observed in ethanol extracts could happen via the cell cycle arrest as previously stated (Harhaji et al., 2008; Hsieh et al., 2002).

Likewise, the aqueous extracts of the fruiting bodies from C. versicolor suppress in vitro 4T1 cell migration and invasion; moreover, these extracts decreased in vivo tumor weight and lung metastasis in BALB/c mice bearing orthotopic 4T1 tumors (Luo et al., 2014). The aqueous extracts of mycelial biomass from T. versicolor and other mushrooms exhibited in vitro cytotoxic effects against human solid tumor cell lines such as A-549 and SW1573 (lung), HBL-100 and T-47D (breast), HeLa (cervix), and WiDr (colon) (Shnyreva et al., 2018). The grouping of aqueous extracts and chemotherapeutic agents (Roca-Lema et al., 2019) or metronome zoledronic acid (mZOL) (Ko et al., 2017) has also been described to increase the biological activity thereof. For example, the mixture of polysaccharide-rich aqueous extracts from T. versicolor and G. frondosa with 5-fluorouracil improved the in vitro cytotoxic effects in LoVo and HT-29 human colon cancer cells (Roca-Lema et al., 2019); the mixing of the aqueous extract from T. versicolor with mZOL avoided in vivo breast cancer propagation, metastasis, and bone destruction (Ko et al., 2017).

Furthermore, a fraction of polysaccharide isolated from the liquid culture of T. versicolor (Tramesan) exhibited in vitro antiproliferative effects in cell lines of murine melanoma B16-F10 (Scarpari et al., 2017), human myeloid (OCI-AML3), and lymphoid (Jurkat) (Ricciardi et al., 2017). This antiproliferative effect of Tramesan is associated with cell cycle arrest and apoptosis induction, although it has also been described that the effect of numerous fungal polysaccharides is associated with oxidative stress (Queiroz et al., 2015). In addition, cell cycle arrest has been assumed to occur by the inhibition of cyclin-dependent kinases and activation of cell cycle checkpoints, which lead to cell death (Khan et al., 2019). Also, in vitro antitumor activity of an intracellular protein-polysaccharide (Wang et al., 2017a) and extracellular polysaccharide (Wang et al., 2017b) obtained from T. versicolor against HeLa cells was estimated. The results showed that the growth inhibitory effect on HeLa cells occurs via cell cycle arrest with cell accumulation in S phase and an increase in apoptotic cells (Wang et al., 2017a). On the other hand, it was shown that tetralin lignans isolated from T. hirsuta displayed in vitro cytotoxic effects in human malignant glioma cells (U87) (Puri et al., 2006).

Moreover, the polysaccharides isolated from T. lactinea (Berk.) Pat exhibited in vitro antitumor activity on HepG-2 and normal hepatocyte L-02 cells, which was evidenced with the decreased cell proliferation and the increased leakage of cytoplasmic lactate dehydrogenase and the number of apoptotic cells (He et al., 2018). Also, it was shown that the PSK isolated from T. versicolor inhibited cell proliferation by cell cycle arrest and induction of apoptosis in the human pancreatic cancer cells BxPC-3, Panc-1, MIA PaCa-2, and AsPC-1 (Rosendahl et al., 2012).

Furthermore, the polysaccharides obtained from the fruiting bodies of T. robiiniophila showed the ability to reduce in vitro cell proliferation in human osteosarcoma U-2 OS cells (Zhao et al., 2015a) and human osteosarcoma xenograft tumor growth in vivo (Zhao et al., 2015b). These polysaccharides induced apoptosis in tumor tissues and U-2 OS cells through a mitochondria-dependent pathway, as demonstrated by the increase in Bax/Bcl-2 ratio, activation of caspase-9 and caspase-3, and cleavage of poly(ADP-ribose)polymerase (PARP). The results indicate that the polysaccharides from T. robiiniophila could be used as a possible chemotherapeutic agent against human osteosarcoma (Zhao et al., 2015a, 2015b). These two studies have shown enough evidence of the anticancer potential in isolated compounds from mushrooms of the genus Trametes to treat human osteosarcoma. Finally, the analysis of this systematic review showed an invaluable potential of extracts and isolated compounds from the genus Trametes as anticancer agents.

Lastly, mushroom β-glucans contain linear β-(1→3) linked backbones with β-(1→6)-linked side chains of varying length and distribution. Some structural variations include 1→4 linkages, α-glucan moieties, protein complexes, and sugar type. Mushroom β-glucans present a great variety of biological activities, highlighting their anticancer and immunomodulatory activity. These properties could be associated with their ability to induce biological responses by binding to membrane receptors. β-glucans can induce the immune system since they are not synthesized by humans and therefore they are recognized as strange agents (Phan et al., 2018).

CONCLUSION

The present systematic review has examined the current evidence on the anticancer activity of chemical compounds from mushrooms of the genus Trametes in human osteosarcoma. Finally, 15 studies were included, in which 6 of them assessed extracts, 8 studies evaluated polysaccharides, and 1 study estimated tetralin lignans of different species of the genus Trametes. The results and analysis of the articles involved in this review have provided enough indication of the anticancer potential of isolated compounds from different species of the genus Trametes. However, studies relating to the anticancer potential of bioactive mushrooms compounds in human osteosarcoma are incipient yet. These findings leave an open gap to continue with studies that help to address this health problem as well as understand the mechanisms by which these natural products have beneficial effects on the treatment of different types of cancer.
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