Tripterygium Wilfordii Extract (Triptolide) and Amygdalin Promotes Cell death in Cancer Cells: True or a Myth

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Abstract Different natural products are known for their use in conventional medicine and especially for their beneficial effect on chronic diseases including autoimmune and cancer. A purified natural extract sample from the Chinese herb Tripterygium wilfordii Hook F (known as Lei Gong Teng or Thunder of God Vine) containing diterpenoids and triepoxides, was associated with significant anti-tumor effects and with encouraging results. Additionally, another natural extract from apricot kernels, Amygdalin (also known as laetrile or vitamin B17) a cyanide-containing substance, has been reported as a potential anti-cancer molecule with numerous contradictions among different published data. For many years different scientist tried to investigate in vivo, in vitro and ex vivo the efficacy of all of these molecules but they all failed in giving clear robust positive conclusions and the opinions are contradictory. Most of the studies were focusing on the apoptotic effects that can lead to the programmed cell death (PCD), a noteworthy mechanism in cancer treatment. The present review summarizes published reports and gives a better understanding of the known abilities as well as the possible role of these specific natural extract molecules in the fight of cancer treatment, cure and prevention.

Keywords: cell death, apoptosis, Triptolide, Amygdalin, Vitamin B17, anti-cancer agents

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1. Introduction

Traditional Chinese Medicine (TCM) using mostly natural products has been used throughout the centuries for the treatment and cure of inflammation, chronic diseases in general including cancer; and for the manufacture of pharmaceutical products aiming to treasure the cure for various diseases of millions of people worldwide. [1,2] “Thunder of God”, one of the Chinese medicinal herbs that belongs to genus Tripterygium, grows usually in the mountainous regions of southeast and southern China. In the 1930’s it was used as insecticide in the Western science and as potential medicinal plant in the 1960’s. The name comes from Charles Wilford, a botanical collector at London Kew Botanical Gardens (1857–1860). He found the plant on the island of Formosa (now Taiwan) in June 1858. [3] The literature review demonstrates encouraging therapeutic potentials of Tripterygium wilfordii Hook F (TwHf) and its natural extract, the Triptolide, in many autoimmune and inflammatory conditions (Figure 1A). [4,5] Different phase 2b clinical trials have been performed investigating the efficacy of TwHf extracts on several diseases such as rheumatoid arthritis (RA), Crohn’s disease and kidney transplantation. [6,7] Previous studies have demonstrated anti-inflammatory and anticancer activity. [8-15] Moreover, Triptolide proapoptotic and antiproliferative activity has also been associated with a numerous cancer cell lines in vitro and in vivo such as: HL-60, T cell lymphoma (Jurkat), U937, OCI-AML3 Kasumi-1 and SKNO-1 cells, human hepatocellular carcinoma SMMC-7721 cells, and cell lines of multiple myeloma, breast, gastric, prostate, lung, oral, colon, pancreatic and cervical cancers, cholangiocarcinoma, and neuroblastoma. [8-15] In vivo trials confirmed the therapeutic activity of Triptolide in a number of model systems including hamster models, human melanoma xenografts, gastric carcinoma, breast cancer, pancreatic cancer, bladder cancer and neuroblastoma in nude mice studies. [16,18] Moreover, Triptolide has been shown to fortify other agents helping as combination with other drugs to improve their cancer treatment abilities. [19,20,21] Some of the recorded side effects were diarrhea, headache, nausea and infertility. As a result, the safety issue was one of the major reasons that led to numerous attempts for the improvement of its biochemical properties including both safety and efficacy. [22,23] The therapeutic indications of TwHf extract can be associated with more than 100 molecules such as diterpenes, triterpenes, sesquiterpenoids, and alkaloids, found in the natural extract samples; and are used for the treatment of various diseases. [24,25,26] On the other hand, a number of these molecular components
were shown to be associated with anti-fertility effects in male animal models. [27,28] Even though advances have been made towards the understanding of the molecular mechanisms of the aforementioned compounds, the precise targets of Triptolide and the major compounds found within the TwHF extract remain unclear. As a result, more precise pre-clinical studies have yet to be performed to ensure safety of the Triptolide molecule as well as a clear understanding of its way of biomechanical action.

Figure 1. Molecular structures of (A) Tripterygium wilfordii Hook F (Triptolide) and (B) Amygdalin (provided by Pubchem)

Amygdalin (vitamin 17) belongs in the nitrilosides molecules family and previously called laetrile (Figure 1B). Furthermore Amygdalin has been reported as a natural anti-cancer extract containing cyanide and it is abundant in the seeds of Prunasin family like apricots, almonds, peaches, apples, and other rosaceous plants. Including in the Prunasin, Armeniacae semen has also been used for the treatment of colorectal cancer, leucoderma, bronchitis, emphysema, asthma, leprosy and pain. [29,30,31] The structure of Amygdalin contains two molecules of glucose, one of benzaldehyde that induces an analgesic action, and one of hydrocyanic acid, that is an anti-neoplastic compound. Over the above actions, Amygdalin has been shown to treat several types of cancer as well as a pain relief. [32,33,34] Moreover, Amygdalin has been demonstrated to selectively induce cancer cells death. [35] The impact of Amygdalin in the prevention and control of cancer has also been analyzed and reviewed. [36,37] It is important to emphasize that due to its cyanide functional group and the potential toxicity, there is a dechognomy among the scientific community for the use of Amygdalin as a cancer treatment. [36,37,38] However, Moertel et al. (1981) revealed that, in humans, intravenous infusion of Amygdalin did not cause cyanideemia nor signs of toxicity. In contrary, the oral administration of Amygdalin resulted in significant blood cyanide levels and in one case, oral Amygdalin in combination with almond extract produced transient symptoms of cyanide intoxication and further increase of blood cyanide as reported by Moertel et al. (1981). [38,39] Additionally, Fukuda et al. (2003) previously reported that Amygdalin and other components of Prunus Persicae seeds have anti-cancer properties. While Kwon et al. (2003) demonstrated that Persicae semen was able to convert the active anti-cancer form from its inactive form [40].

Overall, despite the fact that there is a growing interest regarding the possible anti-cancer properties of Amygdalin, there are no reports proving how it mediates its anti-cancer activity. This short review is based on information collected through the literature review and we will attempt to further our understanding and to answer a crucial question: “Triptolide and Amygdalin promotes cell death in cancer cells: true or a myth”; that stands for decades under strong debate among the scientific community.

2. Triptolide and Amygdalin ‘Friend or Foe’

Triptolide and Amygdalin as potential anticancer agents

Triptolide, as a molecule with anti-cancer activity potential, has attracted the interest of many scientists and researchers. [41] Studies on prostate cancer cells revealed some interesting information. For example, human prostatic epithelial cells derived from normal tissues and adenocarcinomas in primary cultures showed extreme resistance to apoptosis. [41] The function of wild-type p53 is diminished in particular cell lines, due to the fact that the drugs requiring p53 activity to induce cell death are rather ineffective. As a result, the potential properties of Triptolide helped towards its recent water-soluble form (PG490-88) approval for Phase I clinical trials for antitumor activity against prostate cancer (Table 1). [41] Experiments were previously performed to show that
Triptolide had direct effect on both normal and several different cancer cell lines. At low concentration Triptolide inhibited cell proliferation and promoted a senescence-like phenotype. In contrast high concentration of Triptolide increased apoptosis that was not associated with the effects of p53 induced cell death. [41] However inconsistently p53 target genes such as p21WAF1/CIP1 and hdm-2, were reduced, as was bcl-2. [41] A number of preclinical studies suggested that Triptolide could be an effective, preventive as well as therapeutic agent against prostate cancer and that Triptolide might be mediating its effect via a p53 mediated pathway [41].

Table 1. Previously published work on Tripterygium Wilfordii extract

| Trial Design | Results | Randomized | Reference |
|--------------|---------|------------|-----------|
| Phase I clinical trial | Anticancer activities against prostate cancer | *N/A | Taija et al. (2002) [41] |
| in vitro | Promotes apoptosis in laryngocarcinoma cells | N/A | Fei et al. (2013) [42] |
| in vivo | Inhibitory effect on colon cancer | N/A | Zhigang et al. (2009) [43] |
| Clinical trials | Tripterygium wilfordii Toxicity | No | Takes et al. (1997) [51] |
| Clinical trials | Antifertility in Humans | No | Xu et al. (2004) [53] |
| Clinical trials | Renal toxicity | No | Lopez et al. (2005) [55] |
| Clinical trials | Cytotoxicity | N/A | Zhen et al. (1995) [57] |
| in vitro and in vivo | Triptolide is reported with beneficial effects on RA with clinically important side effects | Yes | Little et al. (2001) [71] |
| Clinical trials | | | Cameron et al. (2009) [72] |

*N/A: Not Applicable.

Taking into consideration the fact that the toxicity of Triptolide on cancer cells included apoptosis induction activity, a further examination of the apoptosis induction effect of Triptolide in Hep-2 cells was examined. Triptolide subjected to analysis by flow cytometry induce cells to accumulate in sub-G1 phase in a dose dependent manner and induced Annexin V (AV)-FITC and PI double staining of both early (AV+/PI-) and late apoptotic cells (AV+/PI+). These results strongly indicated that Triptolide efficiently induced apoptosis in laryngocarcinoma cells. [42] Furthermore Triptolide was showed to promote apoptosis that involve both intrinsic and extrinsic pathways. Thus, both activated caspase-8/-9 cleaves the effector caspase-3 to promote cell apoptosis. One of the targets of caspase-3, PARP was also cleaved. These results therefore confirmed that Triptolide efficiently induced apoptosis in laryngocarcinoma cells [42].

Additionally, Triptolide has been reported to reduce growth of primary tumors in nude mice. The in vivo testing of Triptolide on colon cancer highlights Triptolide’s effects. [43] When Triptolide was administered to mice with established primary tumor xenografts, the results were significantly positive. The outcomes showed that Triptolide had a positive inhibitory effect on the growth of all tumor cell lines in a dose-dependent manner. Tumor xenografts demonstrated that Triptolide reduced the levels of IL6R, JAK1 and phosphorylation of STAT3. In contrast Rac1 levels were unchanged. Moreover, the growth of DN17-Rac1 transformed cells were significantly lower than non-transformed tumor cells in nude mice and the CA-Rac1 transformed cells grew faster than non-transformed tumor cells [43].

Amygdalin (laetrile or vitamin B17).

Amygdalin is another molecule under strong debate, for its effectiveness in the viability of prostate cancer cell. In particular, DU145 and LNCaP cells treated with Amygdalin exhibited several morphological characteristics of apoptosis. Amygdalin treatment increased the expression of Bax, a pro-apoptotic protein, and decreased the appearance of Bcl-2, an anti-apoptotic protein, while increasing caspase-3 enzyme activity in DU145 and LNCaP prostate cancer cells. [44] Thus, it could be concluded that Amygdalin can possibly induce apoptotic cell death in human DU145 and LNCaP prostate cancer cells by activating the caspase-3 and down-regulation of Bcl-2 and up regulation of Bax. [44] The current literature review reveals that Amygdalin may offer valuable aid for the treatment of prostate cancers by promoting apoptotic cell death [44].

Table 2. Previously published work on Amygdalin

| Trial Design | Results | Randomized | Reference |
|--------------|---------|------------|-----------|
| in vitro | Morphological characteristics of apoptosis, expression of Bax (proapoptotic protein) | *N/A | Hyun-Kyung et al. (2006) [44] |
| in vitro | Antimicrobial and antioxidant activities against human pathogenic microorganisms | N/A | Moertel et al. (1982) [46] |
| in vitro | Amygdalin down-regulates genes belonging to cell cycle in colon cancer cells | N/A | Hae-Jeong et al. (2005) [49] |
| in vivo | Hazardous in Humans and animals | N/A | Humbert et al. (1977) [83] |
| in vivo | Animal poisoning | N/A | Schmidt et al. (1978) [80] |

*N/A: Not Applicable.

Other evidences demonstrated the in vitro antimicrobial and antioxidant activity of methanol and water extracts of sweet and bitter apricot kernels (Prunus Armeniaca L.) (Table 2). The antioxidant properties of apricot kernels extract were evaluated by determining radical scavenging power; lipid peroxidation inhibition activity and total phenol content measured with a DPPH (2,2-diphenyl-1-picylhydrazyl), via electron paramagnetic resonance (EPR) signals, the thiocyanate method and the Folin method. [45,46,47,48] On contrary, the extracts of the bitter...
kernels, both the water and methanol extracts of sweet kernels have been proved to be associated with antioxidant efficacy. [45,46,47,48] The maximum percent inhibition of lipid peroxidation (69%) and the total phenolic content were detected in the methanol extract and in the water extract of the same cultivar of sweet kernels (Hasanbey). [45,46,47,48] Antimicrobial activities against human pathogenic microorganisms were also tested using the above extracts by a disc-diffusion method.

The effect of Amygdalin in colorectal cancer has also been studied. [49] Microarray studies indicated that Amygdalin downregulated genes belonging to cell cycle category: exonuclease 1 (EXO1), ATP-binding cassette, sub-family F, member 2 (ABCF2), MRE11 meiotic recombination 11 homolog A (MRE11A), topoisomerase (DNA) 1 (TOP1), and FK506 binding protein 12-rapamycin-associated protein 1 (FRAP1). Reverse Transcription-Polymerase Chain Reaction (RT-PCR) analysis confirmed that mRNA levels of these genes were also decreased by Amygdalin treatment in SNU-C4 human colon cancer cells. [49] These findings indicated that Amygdalin could be associated with anticancer effect via down regulation of cell cycle-related genes in SNU-C4 human colon cancer cells. These findings strongly indicate that Amygdalin could be used as a therapeutic anticancer drug [49].

3. Triptolide and Amygdalin as Toxic Agents

Triptolide
Trypterygium has also been reported as a toxic herb possibly causing liver injury, genetic damage, and birth defects. [50,51,52,53,54] However, it is not proven that isolated extracts of Trypterygium could be safe. Thus, Tao X et al (2000) suggested that all forms of herbs extracts have to be avoided by pregnant women, young children, kidney and liver disease patients [54].

A study aimed to evaluate the effect of Triptolide in Rheumatoid Arthritis revealed antiinflammatory effect in men participated in the trial. Mean sperm density and motility were lower in the treatment arm versus the control, while follicle-stimulating hormone was higher in the treatment group. [55,56,57,58,59] However, testosterone levels and libido had been shown without any effect. Similar observations have been reported for related animal studies. [55,56,57,58,59] Furthermore these compounds had direct effect on sperm development as well as testosterone levels, with sperm returning to normal after 6 weeks. However, high quality clinical trials are lacking to confirm efficacy and safety (Table 1) [55,56,57,58,59].

Even though clinical studies demonstrated positive effects of extracts in renal-associated conditions, such as renal transplant and idiopathic refractory nephrotic syndrome, the effects were suggested to be due to immune-modulation rather than direct activity on the kidney (Table 1). [60,61] One out of several clinical trials examined the effect of Triptolide in renal transplant recipients over five years. However, this was not a clinical study. [60] In a separate study, from the same group that lasted more than a year, the effect on sirolimus-induced proteinuria in similar patients was evaluated. [61] Several previous clinical trials, included in a meta-analysis on idiopathic refractory nephrotic syndrome, indicated beneficial effects on laboratory indices such as hypoalbuminemia, proteinuria, edema, and hypercholesterolemia. [62] Further animal and human studies, as well as in vitro models, indicated that “Thunder God Vine” extracts exert effects in autoimmune diseases. Interference in transcription of cytokines, prostaglandin secretion, response of mononuclear cells, generation of cytotoxic T-cells, IL-2 production, and inhibition of T-cell and B-cell proliferation were among the suggested mechanisms. [63,64,65,67] The major immunosuppressive activity was suggested to be due to the effect of diterpenoids, triptolide and tripdiodide, while other chemical compounds such as dihydroagarofurans, alkaloids, tripchlorolides, and triterpenes could also be involved [68,69,70].

Only a very small number of clinical trials have been conducted under appropriate methodological protocols and under specific guidelines.

However, in those few trials that do meet quality protocol criteria, Triptolide was reported with beneficial effects on RA symptoms but was associated with clinically important side effects (Table 1). [71,72] Moreover Tao XL et al (1989, 2002) demonstrated improvement in patient and physician rated tenderness, swelling, and morning stiffness following treatment with Triptolide. Laboratory tests including erythrocyte sedimentation rate, immunoglobulin G, immunoglobulin M, immunoglobulin A, and C-reactive protein were evaluated and showed improvement. [73,74] A clinical trial was performed by in Coldbach et al (2009) and they found a greater effect of the Triptolide extract in treating RA patients over 24 weeks than the sulfasalazine, with similar adverse side effects [75].

Amygdalin
Amygdalin is a cyanogenic glycoside mostly found in apricot kernels, bitter almonds and other seeds. [76] It is commonly known as Laetrile (the synthetized form of Amygdalin) or as vitamin B17; a drug that has been advocated variously as a cure for several types of cancer. [76,77] However none of these claims have been substantiated. The question of whether Laetrile has a positive cancer treatment efficacy is still unclear. [78] Numerous animal studies have been reported showing that Amygdalin has a lack of efficacy (Table 2). No clinical study was able to show Amygdalin to have clear therapeutic effects. [79] On the other hand; Amygdalin has been associated with toxic and lethal side effects in animal and human studies [80-88].

In an earlier study, Amygdalin fed to dogs produced cyanide toxicity when the compound was consumed together with sweet almonds a food containing glucosidase, the enzyme known to hydrolyze Amygdalin to release cyanide. In addition, an observed sign of respiratory, cardiac and neurological impairment was resulted infertility due to cyanide-poisoning. [86,87,88,89] These earlier studies had focused on the acute toxicity of Amygdalin and addressed the potential for chronic cyanide toxicity associated with Amygdalin [86,87,88,89].

Our point of view
Overall, this review shows that a controversy exist with the use of the natural aforementioned extracts and further studies are therefore necessary to determine the true properties of those agents on the treatment of cancer. Moreover, to date those natural compounds were tested in
vitro, in vivo, and ex vivo in both animal and human cancer cell lines. Even though several reports demonstrated positive actions of both Triptolide and Amygdalin that could pave the way for further clinical trials on patients with lethal and terminal malignancies. However, high dosages of these agents may promote side effects and so further studies are required to confirm and determine these effects.

In Conclusion the present review demonstrate the advantages and disadvantages of the use of Triptolide and Amygdalin for the treatment of cancers. Existing therapies on cancer are known to be highly toxic with severe side effects that reduce the quality of life of the patients with no more than 6 months life expectancy. It is more that consoling to proceed with further studies on these bioactive natural molecules. Finally, further experimental tests as well as properly designed randomized, double blind trials have to be performed, in order to conclusively report any possible anticancer efficacy of Triptolide as well as Amygdalin natural agents.

Disclosure

All authors declare no any conflict of interest.

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