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Review Article

ANTI-METASTATIC MECHANISM AND EFFICACY OF BROMELAIN

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ABSTRACT

Bromelain, an enzyme from the pineapple plant has varied pharmacological activities, out of which it shows specific anticancer activity and now is gaining attention regarding this aspect. Medicinal qualities of bromelain include antiedematous; anti-inflammatory, anti-thrombotic, fibrinolytic, immunogenicity and it is used in the treatment of thrombosis and thrombophlebitis, diarrhea, debridement of burns etc. This article reviews the mechanism and efficacy of bromelain in fighting against tumor cells, inspite of it being a natural drug with enzymatic background. Bromelain shows antimetastatic efficacy and inhibits platelet aggregation, growth, and invasiveness of tumor cells. Its effectiveness and safety in cancer treatment has to be considered due to its Selective cytotoxicity. Bromelain being a plant extract, contains various components such as proteinases, peroxidises, phosphatises, protease inhibitors and organically bound calcium. These components might contribute to the variations of bromelain's pharmacological activities. The main aim of this article is to focus the safety and efficacy of this drug in cancer treatment and comparing it with other chemotherapeutic agents.

KEYWORDS: Apoptosis, Anti-angiogenetic activity, Bromelain, Metastasis, Proteolytic Enzymes, Safety.

INTRODUCTION

Pineapple is the common name of *Ananas comosus* (syn. *A. sativus*, *Ananassa sativa*, *Bromelia ananas*, *B. comosa*). Pineapple is the leading edible member of the family Bromeliaceae, grown in several tropical and subtropical countries including Philippines, Thailand, Indonesia, Malaysia, Kenya, India, and China. It has been used as a medicinal plant in several native cultures

Bromelain is a crude extract from pineapple & has been chemically known since 1875 and is used as a phytomedical compound. It is an enzyme that undergoes breakdown of proteins. It is a mixture of substances, mainly composed of two sulfhydril-containing protein-digesting enzymes called proteolytic enzymes or proteases. Bromelain also contains peroxidase, acid phosphatase, several protease inhibitors and organically bound calcium and remains stable over a wide range of pH 2 to 9. Available evidence indicates that bromelain is well absorbed orally with its therapeutic effects being enhanced in a dose dependent manner.

ANTIMETASTATIC MECHANISM

Existing evidence derived from clinical observations as well as from mouse- and cell-based models suggests that bromelain acts systemically, affecting multiple cellular and molecular targets. Bromelain shows antimetastatic efficacy and inhibits platelet aggregation, growth, and invasiveness of tumor cells. In recent years, studies have shown that bromelain has the capacity to modulate key pathways that support malignancy. It is now possible to suggest that the anti-cancer activity of bromelain consists in the direct impact on cancer cells and their micro-environment, as well as in the modulation of immune, inflammatory and haemostatic systems.[1]

Bromelain is an enzyme and this background can be used for anticancer activity. Proteolytic enzymes can be helpful in treating cancer as they help restore balance to your immune system.

Some of the ways proteolytic enzymes can be helpful in the fight against cancer are by boosting cytokines, particularly interferon and tumor necrosis factor, which are very important warriors in destroying cancer cells. Another way by decreasing inflammation is by dissolving fibrin as Cancer cells hide under a cloak of fibrin to

escape detection. Once the cancer cells are "uncloaked," they can be spotted and attacked by your immune system. It is also thought that fibrin makes cancer cells "stick together," which increases the chance for metastases. German studies have shown that systemic enzymes increase the potency of macrophages and killer cells 12-fold.[2] Researchers have now identified several cancer-killing mechanisms of bromelain, including deactivation of the key gene signal NF-kappaB and induction of the autophagy process that causes the cancer cell to self destruct. Another recent study in human breast cancer cells showed that bromelain could activate the process of autophagy in cancer cells, causing them to "eat themselves" and die.[3] Autophagy is a normal house cleaning process in healthy cells. In cancer cells the process is hijacked. The fact that bromelain can turn the tables on cancer cells is quite interesting.[4] Recent studies have shown that bromelain has the capacity to modify key pathways that support malignancy.

Presumably, the anticancerous activity of bromelain is due to its direct impact on cancer cells and their microenvironment, as well as on the modulation of immune, inflammatory, and haemostatic systems.[1] Most of the in vitro and in vivo studies on anticancer activity of bromelain are concentrated on mouse and human cells, both cancerous and normal, treated with bromelain preparations.

In an experiment conducted by Beez et al chemically induced mouse skin papillomas were treated with bromelain and they observed that it reduced tumor formation, tumor volume and caused apoptotic cell death.[5]

In one study related to bromelain treatment of gastric carcinoma Kato III cell lines, significant reduction of cell growth was observed[6] while in another study bromelain reduced the invasive capacity of glioblastoma cells and reduce novoprotein synthesis.[7] Bromelain is found to increase the expression of p53 and Bax in mouse skin, the well-known activators of apoptosis.[1] Bromelain also decreases the activity of cell survival regulators such as Akt and Erk, thus promoting apoptotic cell death in tumours. Different studies have demonstrated the role of NF-κB, Cox-2, and PGE2 as promoters of cancer progression.

Evidence shows that the signaling and over expression of NF-κB plays an important part in many types of cancers.[8,9]

Cox-2, a multiple target gene of NF-κB, facilitates the conversion of arachidonic acid into PGE2 and thus promotes tumour angiogenesis.[10,11]

It is considered that inhibiting NF-κB, Cox-2, and PGE2 activity has potential as a treatment of cancer. Bromelain was found to down regulate NF-κB and Cox-2 expression in mouse papillomas and in models of skin tumourigenesis.[12] Bromelain was also shown to inhibit bacterial endotoxin (LPS)-induced NF-κB activity as well as the expression of PGE2 and Cox-2 in human monocytic leukemia and murine microglial cell lines. [13]

Bromelain markedly has in vivo antitumoural activity for the following cell lines: P-388 leukemia, sarcoma (S-37), Ehrlich ascetic tumour, Lewis lung carcinoma, and ADC-755 mammary adenocarcinoma. In these studies, intraperitoneal administration of bromelain after 24 hours of tumour cell inoculation resulted in tumour regression.[5]

Bromelain with similar regulating actions has shown protective properties on tumour cell growth retardation & Lung metastasis.[6] Batkin, while studying the antimetastatic effect of Bromelain with or without its proteolytic & anticoagulant activities in animal model of Lewis Lung Carcinoma, reported significant reduction in total number of metastasis in both active and inactive forms of bromelain as compared to control groups. A study result reported by researchers of Queensland Institute of Medical Research (QIMR) reports discovery of two new proteins CCS & CCZ which were found to block growth of broad range of tumour cells in breast, lung, colon, ovarian and melanoma. Although more studies are to be done on them.[18]

SAFETY IN CANCER CHEMOTHERAPY

Chemotherapy drugs are, by their very nature, extremely toxic and typically work against your body's natural ability to fight cancer, e.g. destroying host immunity instead of supporting it. One of the biggest drawbacks to chemotherapy is the fact that it destroys healthy cells throughout your body right along with cancer cells, a "side effect" that often leads to accelerated death, not healing. Another devastating side effect of chemotherapy is the way it actually supports the more chemo resistant and malignant cell subpopulations within tumors (e.g. cancer stem cells), both killing the more benign cells and/or senescent cells within the tumor that keep it slow-growing, or even harmless. A handful of natural compounds have been discovered, however, which exhibit an effect called "selective cytotoxicity." This means they are able to kill

cancer cells while leaving healthy cells and tissue unharmed. This type of cancer treatment is intelligent, targeted and will not result in the death of the patient from "collateral damage" in what is increasingly a failed war not against the cancer being treated, but the patient's own irreversibly devastated body. One such compound is bromelain, an enzyme that can be extracted from pineapple stems. Research published in the journal *Planta Medica* found that bromelain was superior to the chemotherapy drug 5-fluorauracil in treating cancer in an animal study. Researchers stated that the antitumoral effect of bromelain was superior to that of 5-FU [5-fluorouracil], whose survival index was approximately 263 %, relative to the untreated control.[15,17]

Bromelain worked without causing additional harm to the animals. The chemo drug 5-fluorauracil, on the other hand, has a relatively unsuccessful and dangerous track record despite being used for nearly 40 years. As written by Green Med Info: "As a highly toxic, fluoride-bound form of the nucleic acid uracil, a normal component of RNA, the drug is supposed to work by tricking more rapidly dividing cells, which include both cancer and healthy intestinal, hair follicle, and immune cells, into taking it up, thereby inhibiting RNA replication enzymes and RNA synthesis[16]. Selective cytotoxicity is indeed a property that is only found among natural compounds; no chemotherapy drug yet developed is capable of this effect. This proves safety and lesser side effects of bromelain, a boon from nature.

CONCLUSION

Bromelain can be a promising natural supplement for the development of oral enzyme therapies for oncology patients. Bromelain is a multiaction enzyme. However its safety and efficacy as anticancer agent is appreciable and research should be progressed in the view. Abundant source & easy availability of bromelain from pineapple are added advantages for its use in various treatments, Cancer being the prominent one.

The science now supports the use of bromelain as part of a natural support strategy for any cancer treatment or for prevention. As more research is done the precise mechanisms of bromelain in the war on cancer will be better understood. The data to this point indicates that bromelain is yet another nutrient, like green tea, curcumin, quercetin, resveratrol, and tocotrienols, that are able to tell the difference between cancer cells and healthy cells, helping to kill the former while assisting the survival of the healthy cells.

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