BROMELAIN: ITS USE IN PREVENTION AND TREATMENT OF CARDIOVASCULAR DISEASE PRESENT STATUS

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Introduction

Bromelain is the enzyme system of the pineapple plant. Although it has been known for many years, it became commercially important only in 1957 when it was first manufactured on an industrial scale in Hawaii. Since then, bromelain has been evaluated for its use in medicine and considerable research has been carried out to study its composition and properties (Verlinden, et al., 1977; Cooreman, et al., 1976, and Dupaigne, 1975).

During the past 15 years, approximately 400 papers have been published describing the use of bromelain in

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clinical practice (Taussig, et al., 1975). A large number of seemingly unrelated ailments respond favorably to bromelain treatment. The list comprises gastrointestinal, respiratory, gynecological, most inflammatory and cardiovascular diseases, debridement of burns, cancer therapy and many others.

Although many of the publications are not controlled double-blind studies, the results obtained on a very large patient population are so unequivocal that there can be no doubt of the validity of the reported findings.

Cardiovascular Applications

One of the most recent, and probably most important, applications of bromelain is its use in cardiovascular and circulatory diseases. This is a new field of application and relatively little has been published on the subject; although, this Journal recently published anti-anginal cardiovascular findings by Hans Nieper.

The purpose of this paper is to summarize what is known at this time of bromelain's application in cardiovascular diseases in order to stimulate interest and further research. The great advantage of using bromelain is that its margin between effective dose and toxicity is very wide. While the levels of efficacy and toxicity for most drugs used in this field are very close, bromelain is practically nontoxic (there is no LD50 up to 10 g/kg) (Moss, et al., 1963); therefore, it can be used in any dose without risk.

Research carried out during the past six years indicates that bromelain prevents aggregation of human blood platelets in vivo and in vitro, it prevents or minimizes the severity of angina pectoris and TIA attacks, and it is used successfully in the treatment or prevention of thrombosis and thrombophlebitis. A recent study also describes bromelain's effect in breaking down cholesterol plaque. Recently one of the authors (H.N.) has found in phase contrast studies that the blood serum of patients who took high doses of bromelain, after two hours had a potent fibrinolytic activity. If administered for an extended time, bromelain decreases the blood pressure of hypertensive subjects to normal levels.

Inhibition of Blood Platelet Aggregation

It has been reported previously that several proteolytic enzymes like trypsin, fungal and bacterial proteases, as well as papain and bromelain, prevent platelet aggregation (Sano and Yokoyama, 1971).

The first significant contribution to this subject was made by Heinicke, et al. (1972). In their study the tendency for aggregation of blood platelets, stimulated by ADP of susceptible subjects, was decreased after oral administration of bromelain. The tests were carried out on volunteers, some of whom had a history of heart attack or stroke. Heinicke's results are shown in Figure 1. Twenty subjects were treated with oral bromelain (Ananase-100[1]). The unshaded bars show platelet aggregation values prior to oral administration of bromelain, and the shaded bars indicate values after administration.

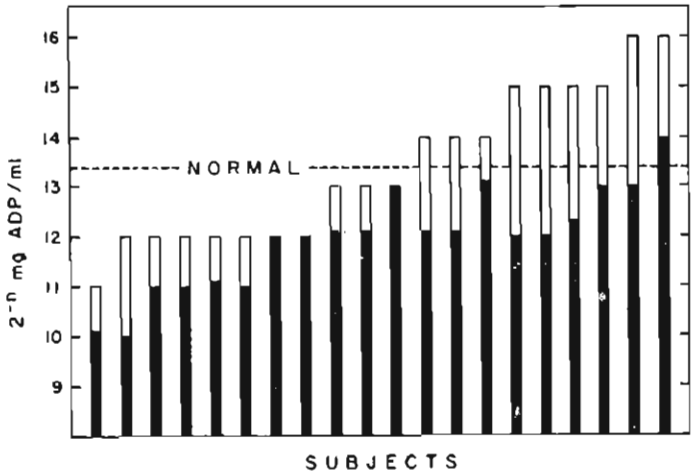

Figure 1. Platelet aggregation before and two hours after bromelain administration (Heinicke, et al., 1972).

Other studies carried out with human platelets in vitro by Morita, et al. 1978), and Taussig, et al., (1978), indicate that bromelain inhibits platelet aggregation stimulated by most conventional agents like ADP or epinephrine, as well as by prostaglandin precursors like archidonic acid or endoperoxyde analog. Their results suggest that bromelain acts as a dose-dependent, selective inhibitor of those prostaglandins which are responsible for the aggregation of blood platelets under certain pathological conditions.

[1]ANANASE-100 (W. H. Rorer, Philadelphia) contains 100,000 Rorer Units = 40 mg bromelain per tablet.

Livio, et al. (1978), found also that bromelain prevents aggregation of rat platelets both in vivo and in vitro.

Coronary Heart Disease and Angina Pectoris

When Nieper administered 400-1000 mg bromelain per day to 14 patients with angina pectoris, the symptoms disappeared in all patients within four to 90 days, depending on the severity of coronary sclerosis. The author attributes the effect to bromelain's ability to break down fibrinous plaques (Nieper, 1978).

The anti-anginal effect of bromelain can be detected already after one to five hours. It is presumed that additional mechanisms are involved in the process, like increased vessel wall permeability for oxygen and nutrients, increase of blood fluidity and deformability of red blood cells. These were discussed elsewhere by Nieper who defined this effect of bromelain initially as a "desludging effect."

Similar effects were reported by persons with angina pectoris who took 500-700 mg bromelain daily for non-angina related reasons. As long as bromelain was administered, no angina symptoms appeared and no sublingual nitrates were required. After discontinuing bromelain for a period of time, the angina attacks reappeared, mainly after stress situations. They disappeared and remained absent after resumption of bromelain treatment.

A drastic reduction of incidence of coronary infarct was described by Nieper (1977) after administration of potassium and magnesium orotate with bromelain. Doses between 120-400 mg bromelain per day were used. After a two-year period, two deaths were recorded among 140 patients and in another group of 76 patients, two

deaths were reported during a four-year period. Here we deal with a synergistic action and there is no way to determine at this time how much of the effect is due to bromelain or the orotates. The fact is that bromelain is needed to obtain dramatic results.

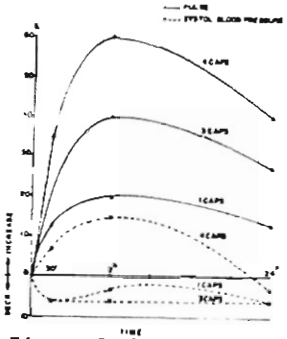

Figure 2. Variation of blood pressure and heart rate infunction of oral bromelain administration (Gutfreund, et al., (1978).

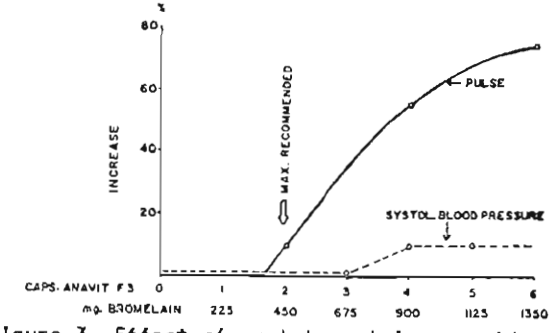

Figure 3. Effect of oral bromelain upon blood pressure and heart rate two hours after administration (Gutfreund, et al., 1978).

Effect of Bromelain on Blood Pressure

Persons with high blood pressure who were taking bromelain for various problems for extended periods of time noticed invariably a slow and steady decrease of their blood pressure to normal levels. Gutfreund, et al. (1978), investigated the effect of large amounts of oral bromelain administered in one dose on blood pressure and heart rate of hypertensive patients. The test was carried out with Anavit-F3[2]. Twenty patients, ranging between 33 to 73 years of age, were involved in the test. The dose was increased gradually from one to eight capsules (to 1800 mg bromelain), which is four times the maximum recommended amount to be taken at one time. Each patient served as his/her own control. Some of the results are shown in Figure 2 and Figure 3.

[2]ANAVIT-F3 (C.C.I., Honolulu, Hawaii) contains 230 mg bromelain per capsule.

At normal doses (1-2 capsules), the blood pressure shows a slight decrease and increases only slightly by overdoses (Figure 2). At the same time, the heart rate increases with increasing dose. This increase reached 80% of the original value at eight capsules (this curve is not shown). Bromelain reaches its maximum effect in the system after two hours (Figure 2) and decreases gradually, but even after 24 hours there is a detectable residual effect. Figure 3 shows the two-hour readings. The results are interpreted as an indirect vasodilator effect of bromelain. The failure of the tachycardia to be accompanied by hypertension may perhaps reflect the balanced effects of increased stroke volume and decreased peripheral resistance, a prostaglandin E_1-or prostacyclin-effect.

Periferic Venous Diseases

In an earlier study, Giacca (1965) describes the effect of bromelain on periferic venous diseases. His results are summarized in Table 1. Among 11 patients with thrombophlebitis between age 44 to 72, eight (72%) showed excellent to good results. No side effects were noticed. Giacca's tests were carried out in 1964. At that time only Ananase, with a bromelain content of 20 mg per tablet, was available. Giacca administered four to eight tablets a day, corresponding to 60 to 160 mg of bromelain. We now know that this dosage is inadequate for most bromelain applications. According to present experience, at least 400 to 800 mg daily doses of active bromelain are needed to achieve consistent results.

Clinical observations made by one of us (H.N.) indicate that patients with recurrent thrombophlebitis can be treated continuously for years without any decrease of response to bromelain.

Effect of Bromelain on Cholesterol-Protein Binding

Chen reports that bromelain breaks down arteriosclerotic plaque in rabbit aorta in vivo and in vitro (Chen, 1975). His work is the first defacto evidence for this effect, suspected by many researchers previously. It might be the cause of the "pipe cleaning" effect referred to by Nieper. Chen's findings are important enough to warrant further study.

Table I: Effect of oral bromelain on periferic venous diseases (Glacca, 1965).

Nr	Name	Sex	Age	Diagnosis	Treatment: (Ananase) Bromelain 20mg/abl.	Result*
1.	MA	F	72	Thrombophlebitis (+gastr. neoplasia)	6/day for 1 week	++
2.	RC	F	70	Thrombophl. (+rheumat. arthritis)	4/day for 5 days	++
3.	SL	F	44	Superficial thrombophle.	8/day	+
4.	DA	F	50	Superficial thrombophle.	8/day for 10 days	+
5.	BA	F	40	Phlebothrom. right inf. limb+varicos	8,6,4/day for total 30 days	+
6.	BG	M	68	Acute thrombophleb. left lower limb	6/day for 10 days	++
7.	AF	F	63	Acute thrombophleb. (+hemiparesis)	8/day for 4, 6/day for 10	+
8.	CT	F	72	Acute thrombophl. (+prev. gastr. res.)	6/day for 7 days	++
9.	DR	F	--	Superfic. acute thrombophl. (polyarthr)	6/day for 7 days	+
10.	DMD	F	49	Thrombophleb. (+gastr. res. -ulcer)	-	-
11.	CG	M	64	Recid. thrombophleb. (Pulmon. Infarct)	6/day for 5; 4/day for r	-

* Excellent: ++ Good: + Poor: -

About Bromelain and its Possible Mechanism of Action

Commercial bromelain, including the pharmaceutical grade, is not a chemically homogenous substance. Bromelain's main component is a sulphydryl protease with two proteolytically active components which can be separated by chromatography (Morita, et al., 1979). The protease is a glycoprotein. Bromelain contains further a peroxydase, acid phosphatase, several protease inhibitors (Perlstein, et al., 1973) and organically-bound calcium. If bromelain is purified by various methods, the result is a potent protease, with low physiological activity. Thus, we have to make a distinction between proteolytic and physiological activities which are not necessarily parallel (Taussig, et al., 1978).

The mechanism of action of bromelain is not fully understood presently. There is factual and circumstantial evidence suggesting that bromelain has a selective dose-dependent inhibitory action on certain prostaglandins. It inhibits the E_2-type prostaglandins (only partly, not completely like aspirin or indomethacin) (Vane, 1974). These are the inflammatory platelet-aggregating, vasoconstricting prostaglandins. On the other hand, bromelain seems to have no effect - or possibly even stimulates - the biosynthesis of the E_1- type prostaglandins (Felton, 1977) (the anti-inflammatory, vasodilator, platelet aggregation inhibiting ones. In a diseased organism, the PGE_2-type prostaglandins are increased manyfold above the normal level and create problems associated with blood vessel injuries, inflammation, etc. By decreasing the PGE_2-type prostaglandins to a normal level, bromelain might re-establish the balance between the two types of prostaglandins with opposite effect. It is certain that bromelain does not act directly on prostaglandins (arachidonate cascade). It acts indirectly by breaking down fibrinogen into small peptides with physiologic activities (Livio, et al., 1978). These peptides inhibit blood platelet aggregation via the prostaglandin system. Bromelain also acts directly on fibrin, hydrolyzing it as shown recently by Nieper and others.

It is not known at this time which is the active factor in bromelain - or if there is any single one. There is a good possibility that the beneficial effects of bromelain are due to multiple factors; some having an active role, others might act as stabilizers. The main reasons why bromelain has not gained more attention in the past are that its mechanism of action has not been fully elucidated and that it is not known with certainty which of its components is responsible for its physiological activity. There are, however, several important considerations in favor of bromelain:

1. It inhibits blood platelet aggregation, reduces high blood pressure and minimizes thus the risks of cardiac infarct and stroke.

2. As long as bromelain is administered, it produces the effects described. Its individual components, if separated and/or purified by conventional methods, are physiologically inactive.

3. The attractiveness of using bromelain is its lack of side effects. While most drugs have a very narrow margin between effective dose and toxicity, this range with bromelain is very wide. Therefore, it can be used without concern in the

useful dose range of 200 to 1000 mg.

4. Being essentially a protein, bromelain is easily metabolized as any dietary protein; this might be the cause of absence of side effects.

5. In most of its applications, bromelain is administered orally and is even more effective if used preventively.

As with many other substances, especially foods like strawberries, eggs, milk, etc., a very small segment of the population may be allergic to bromelain. These would be persons who also show allergic reactions when eating pineapple. Therefore, this remote possibility must be taken into consideration when bromelain is administered for the first time.

One final word of caution. Since bromelain is a product derived from a natural source, it has been demonstrated that different sources with the same proteolytic activity have varying physiological activities (Taussig, et al., 1978). Thus several bromelain samples from Taiwan and Brazil had much lower physiological activities (as measured by inhibiting ADP-induced blood platelet aggregation) than bromelain of the same proteolytic activity made in Hawaii. Furthermore, if processed into a product, bromelain can be easily deactivated by improper processing or storage conditions. This is the reason why many commercial preparations display lower or much lower potencies than indicated on their label. Therefore, in order to insure proper performance, increased emphasis should be put on the use of a highly active and stable bromelain preparation.

Heart attack and stroke are the main killers of modern man as shown in Figure 4. If one considers the benefits derived from bromelain, plus the lack of side effects, then look at the alternatives, increased attention to bromelain is certainly warranted.

Summary

The effect of bromelain on blood platelet aggregation, blood pressure, thrombosis and thrombophlebitis are described. Bromelain also breaks down cholesterol-protein binding in vivo and in vitro.

A short description of the composition of bromelain and a hypothesis on its mechanism of action is presented.

Due to its effects and its complete safety, bromelain has all the attributes to play an important role in cardiology in the future.

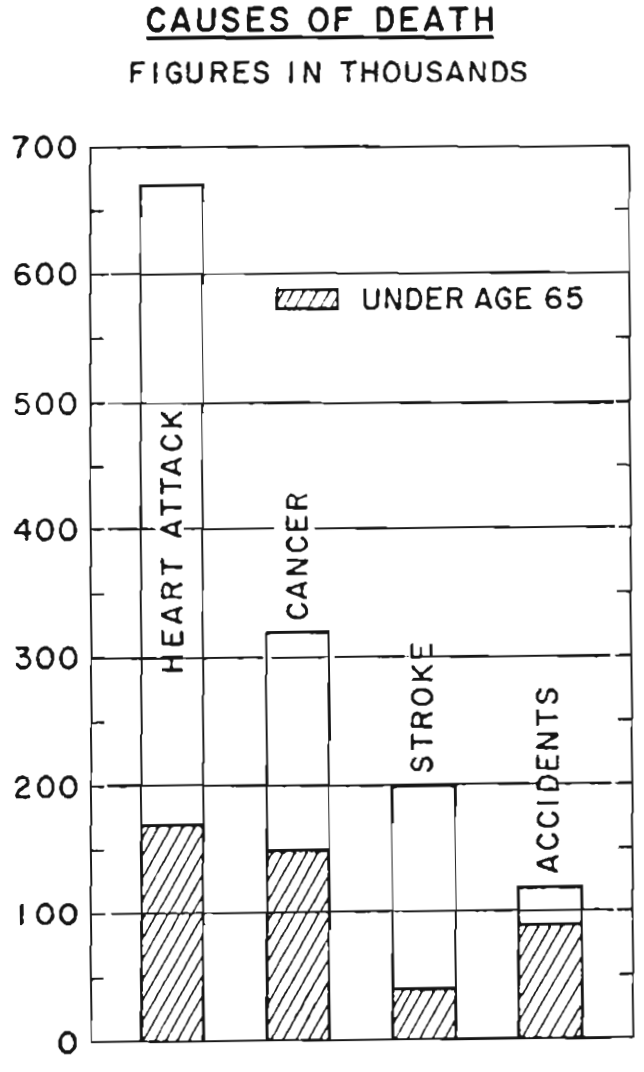

Figure 4. Annual mortality rates in the United States (American Heart Association, 1972).

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