The Natural Products in Protection against the most Important Pathological Changes in Human Metabolism

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Abstract: *Inflammation in joint*: The liberation of phospholipids from cell membranes represents the first step of inflammation cascade. By action of phospholipase A2 is split of the arachidonic acid. Free arachidonic acid is than metabolised by two enzymes: 5-lipooxygenase and 2-cyclooxygenase to generate the group of prostanoids and leukotrienes which are the first active proinflammation compounds, starting the whole proces of inflammation. We verífied, that 27 flavonoids and flavans, contained in American patent Univestin are really able to interrupt this pathway by inhibition both of those enzymes. All these flavonoids are naturally occurring chemicals, which give color to plants and are found in plants, fruits, grains, nuts and vegetables. Theirs antioxidant capacity eliminates the action of Cyt P450 also and prevents to origine of epoxides. *Cancerogenesis*: Inositolhexaphosphate (IP6) is found in substantial amounts in whole grains, cereals, legumes, nuts and seeds. As well as inositol, IP6 is contained in most mammalian cells, wherein they are important in regulating vital cellular function such as signal transduction, cell proliferation and differentation. Inositol and IP6 are contend in product Inocell and there is additional evidence that inositol alone may further enhance the anti-cancer effect of IP6. Beside decreasing cellular proliferation IP6 also causes differentation of malignant cells ofen resulting in a conversion to normal phenotype, what leads to starting of apoptose in those cells. Inocell greatly enhances NK cell activity, regulates cell growth and has very strong antioxidant capacity. The suggestion we can demonstrate on succesfful efects of Inocell in concrete causes of patients with various types of cancerogenesis. *Peptic ulcer disease and gastric cancer*: The ability of *Vaccinium macrocarpon*, the North American cranberry, to prevent bacterial adhesion has been used to advantage in the prevention of urinary tract infections and has recently been described for the prevention of adhesion of bacteria responsible for oral infections and stomach ulcers as well in *Helicobacter pylori*.

Keywords: inflammation; Univestin; Comfort-G; flavonoids; flavans; cancerogenesis; inositolhexaphosphate; inositol; *Helicobacter pylori*; cranberries

INTRODUCTION

From the point of morbidity and mortality they are discovered three areas of pathological changes leading to fatal disorder of human metabolism. They are: inflammation, cancerogenesis and damage of digestive tract epithel. The aim of this paper is to show different natural products, which can play very important role in the protection against named disorders. All our suggestion vere verified by the recent clinical studies.

METHODS

Comfort-G was given to the group of ten patients, m/f ratio 4/6, year: 27–79 in prescribed dose (Posology: Adults: 1 capsule twice a day, the product is not recommended to children, juveniles up to 18 year) during one month.

The molar per cent of arachidonic acid were measured by gas chromatography analysis. Gas chromatographic analyses of FAME were performed on the fused-silica capillary column

DB-WAXETR 30 m × 0.32 mm I.D. (J&W Scientific, USA).

What above Inocell, it is food supplement, containig equal amount of inositol and inositohexaphosphate. Inocell was given to the group of various patients, suffering by carcinoma in dosis, coresponding the step of illness developing.

The Barny's cranberry juice was given to ten patients with positive results of *Helicobacter pylori* infection in dose of 15 ml of juice/day.

RESULTS AND DISCUSSION

Inflammation in joint

We present the result of arachidonic acid measurement in synovial fluid and serum of the group of patients. We found the statistically important difference in molar per cent of AA both in synovial fluid and serum (Table 1).

Table 1. Increase of arachidonic acid (AA) concentration in synovial fluid and serum

	Time		
Synovial fluid	0	4.28 ± 0.22	
	31	7.25 ± 0.56	$P < 0.001$
Serum	0	4.83 ± 0.86	
	31	6.23 ± 069	$P < 0.01$

The effect of inhibition of prostaglandins or leukotrienes production can be expressed by the increase of concentration of arachidonic acid in serum and synovial fluid of damaged joints. The increased values of AA both in serum and especially in synovial fluid are the result of competitive inhibition of following steps of AA pathway, connecting with prostaglandins or leukotrienes production. A competitive inhibitor need not be structurally related to the substrate. Once bound, the enzyme cannot convert the inhibitor to products. Univestin (in EU market Comfort-G) acts to inhibit both COX-2 and 5-LO enzymatic activity directly in the joint via interaction with the enzyme (Table 2).

While the COX pathway has been the focus of attention over the last few years, not as many are aware of the LO pathway and its importance in the relief of joint pain. The LO pathway is a parallel inflammatory pathway to the COX pathway in which AA is converted leukotrienes, the strongest chemotactic agents in the body that cause the accumulation of cells and fluid in damaged joints. Leukotrienes (LT), however, are a group of pro-inflammatory lipid mediators that are implicated in the pathogenesis and progression in atherosclerosis.

For treatment of arthrose, which resulted by this pathway, the nonsteroidal antirheumatic drugs were generaly used (NSAID). Table 2 shows that these drugs have practically no effect on the 5-LO pathway. The stay resulted under the conditions of long time administration by named drugs in progression of atherosclerosis really.

Table 2 shows additionally that only the inhibitors from the lower part of the table are able to inhibit 5-LOX activity. This finding presents the fundamental point of view by choice between NSAID drugs and these natural products as Univestin is. Baicalin and catechin are the most active flavonoids, which are containing in Univestin. The inhibition effect is in Table 2 expressed as the lowest concentration of inhibitors, (Vecka *et al*. 2007).

Table 2. Inhibition effect on enzymatic activity of cyclooxygenase (COX-1 and COX-2) and 5-lipoxygenase (LOX)

Compound	IC50		
	COX-1	COX-2	LOX
Celecoxib	1.13	0.04	/
Refecoxib	1.9	0.5	/
Indomethacin	0.028	1.68	/
Flurbiprofen	0.29	2.56	/
Ibuprofen	1.03	14.5 /	
Aspirin	1.67	278	/
Nexrutine™	0.56	/	/
Licofelone	0.16–0.21	0.18–0.23	0.18–0.23
PGV20229	7	0.22	8
Chrysin	5	5 1	8
Quercetin 1	6	16	3.5
Baicalin	0.99	0.67	9.5
Catechin	0.38	1.45	4.8
Comfort-G	0.45	1.02	3.8
Green tea extract	0.18	1.56	/

IC50 – concentration of inhibitor (in μmol/l) need for the 50% loss of enzymatic activity; / – no activity

Cancerogenesis

Chemoprevention is considered a rational strategy for dietary approaches to prevention of cancer. Multiple lines of evidence suggest that many of our dietary principles are able to intervene in the multistage carcinogenesis process and phytic acid (inositol hexaphosphate, IP6), a phytochemical present in a variety of plant species, has been shown to prevent various cancers, including those of the mammary gland, colon and liver. However, the mechanism of chemoprevention by IP6 has not been fully elucidated. Inositolhexaphosphate (IP6) is found in substantial amounts in whole grains, cereals, legumes, nuts and seeds. As well as inositol IP6 is contained in most mammalian cells, wherein they are important in regulating vital cellular function such as signal transduction, cell proliferation and differentation.

Inositol and IP6 are the content of product Inocell and there is additional evidence that inositol alone may further enhance the anti-cancer effect of IP6.

Inocell protect human metabolism against cancer

A brief summary describing what is presently known about how Inocell works is below:

1. Helps to normalise cell physiology
2. Natural killer activity enhancer
3. Supports tumor suppresor gene activity
4. Inhibits inflammation
5. Potent antioxidant
6. Enhance apoptosis
7. Inhibits metastasis

The following table presents results of our effort to support the cancerogenesis treatment in concrete patients (Table 3).

Based on recent information concerning a possible pathway of Inocell anticancer activity we found two claims which are not fully elucidaded also. Vucenik *et al*. (2004) hypothesised that IP6 reduces tumor growth by inhibing angiogenesis becouse angiogenesis depends on the interaction between endothelial and tumor cells it was found that IP6 has effect on both type of cells. Dorsey *et al*. (2005) found that IP-6, a phytoestrogen, has estrogen receptor (ER) binding capabilities that are not known to cause cellular proliferation in hormone sensitive cells. It is hypothesised that IP-6 can induce competitive inhibition with estrogen for estrogenic binding sites on cancer cells resulting in decreased proliferation. Additionaly Andrew *et al*. (2007) studied the effectivity of class I phosphoinositide 3-kinases (PI3Ks). These enzymes are well-established signal transduction enzymes that play an important role in the mechanisms by which a wide variety of cell surface receptors control several cellular functions, including cellular growth, division, survival, and movement. Class IB PI3K (also known as PI3Kgamma) allows fast-acting, heterotrimeric GTP-binding protein-coupled receptors to access this pathway. Activation of class IB PI3K results in the rapid synthesis of phosphatidylinositol-3,4,5-trisphosphate [PI(3,4,5)P3] and its dephosphorylation product, PI(3,4)P2, in the plasma membrane. These two lipid messengers bind to multiple, pleckstrin homology (PH) domain-containing effectors, **whievelopment???** of several inflammatory pathologies in mouse models of human inflammatory disease. These results suggest small molecule inhibitors of class IB PI3K may represent a novel class of therapeutic agents that may complement existing anti-inflammatory treatments.

Peptic ulcer disease and gastric cancer

Helicobacter pylori infection is a major cause of peptic ulcer disease and gastric cancer. This study postulated that cranberry juice would be effective

Table 3. Example of casuistics

Gender F/M and age	Tumor in tissue	Time of administering of Inocell	Today's state
M 65	lung	4 years	no carcinoma
F 63	breast	2 months	decreasing ca from 7 mm to 1 mm
M 65	brain	5 years	decresing of ca and calcification
M 52	larynx	1 year	no carcinoma
F 66	breast	2 years	no carcinoma

Table 4. Subjective mitigating of stomach troubles with and without cranberry juice

	Female	Male
With cranberry juice		
After 3 days of ATB treatment	7	3
After 5 days of ATB treatment	5	2
After 7 days of ATB treatment	1	2
Without cranberry juice		
After 3 days of ATB treatment	1	2
After 5 days of ATB treatment	6	1
After 7 days of ATB treatment	7	3

Table 5. Evaluation of influence of cranberry juice from the point of view of Hb infection relapse

	Female	Male
After three months relapse		
With cranberry juice	3	0
Without cranberry juice	6	2

in the suppression of *H. pylori* in an endemically infected population at high risk for gastric cancer. Antibiotic treatment does not always inhibit or kill H. pylori with potential for antibiotic resistance Lin *et al.* (2005).

Following tables show amelioration of treatment in relation to presence or absence of cranberry juice (Tables 3 and 4).

The combination of ATB treatment with cranberry juice resulted in:

1. Time reducing of subjective troubles of patients.
2. Lowering of cases of relapse.

CONCLUSION

This short overview suggests that using of natural products in treatment of various illnesses can be very effective. With a numerous patients, suffering by those diseases we hope that the suggestion of our findings discovere the way of this form of activity for physicians in area of sopphysticated medicine too.

References

Andrew S., Stephens L.-R., Hawkins P.-T. (2007): PI3K class IB pathway. Science's STKE, **9**: 407.

Dorsey M., Benghuzzi H., Tucci M., Cason Z. (2005): Growth and cell viability of estradiol and IP-6 treated Hep-2 laryngeal carcinoma cells. Biomedical Sciences Instrumentation, **41**: 205–210.

Lin Y.T., Kwon Y.I., Labbe R.G., Shetty K. (2005): Inhibition of *Helicobacter pylori* and associated urease by oregano and cranberry phytochemical synergies. Applied and Environmental Microbiology, **71**: 8558–8564.

Vecka M., Prokeš L., Tvrzická E., Karpaš K., Pernický L., Pfleger R., Votruba M. (2008): Protizánětlivý účinek flavonoidů z přípravku Comfort-G a změny metabolismu kyseliny arachidonové. Klinická biochemie a metabolismus, **16**(37): 27–33.

Vucenik I., Passaniti M.I., Vitolo K., Tantivejkul P., Eggleton A.M. (2004): Anti-angiogenic activity of IP6. Anticancer Research, **24**: 3477.