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An association of boswellia, betaine and myo-inositol (Eumastós®) in the treatment of mammographic breast density: a randomized, double-blind study

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Abstract. – OBJECTIVE: Mammographic breast density is a recognized risk factor for breast cancer. The causes that lead to the proliferation of the glandular breast tissue and, therefore, to an increase of breast density are still unclear. However, a treatment strategy to reduce the mammary density may bring about very relevant clinical outcomes in breast cancer prevention.

Myo-inositol is a six-fold alcohol of cyclohexane, has already been proved to modulate different pathways: inflammatory, metabolic, oxidative and endocrine processes, in a wide array of human diseases, including cancer and the genesis of mammary gland and breast diseases, like fibrosis, as well as metabolic and endocrine cues. Similarly, boswellic acid and betaine (trimethyl glycine) both inhibit inflammation and exert protective effects on breast physiology.

Based on this scientific background, we hypothesized that a combination including, boswellic acid, betaine and myo-inositol would be able to reduce breast density working on different pathways.

PATIENTS AND METHODS: In this study, seventy-six premenopausal women were randomly assigned to the placebo and the experimental drug arms (Eumastós®) for six months.

RESULTS: After 6 months of treatment, statistically significant difference between the two groups was recorded on the breast density reduction (60% *vs.* 9%), using mammographic as well as ultrasound examination.

CONCLUSIONS: Preliminary data collected here with support the starting assumptions, that the association comprising boswellic acid, betaine and myo-inositol significantly reduces mammary density, providing the first evidence for a new and safe approach for the management of mammographic density treatment.

Key Words:
Mammographic density, Breast density, Boswellic acid, Betaine, Myo-inositol.

Introduction

Nowadays a high breast density is a recognized risk factor for breast cancer. It is assessed by mammography and expressed as the percentage of the breast area that is occupied by radiologically dense tissue. Several studies show that women with a densest breast have a 4-6 fold increased risk of breast cancer compared to women with the least dense breast[1-3].

The mammographic density reflects variations in breast tissue composition[4]. A number of studies investigated the histopathological composition of breast dense tissue correlating the results with mammographies, but it is not yet completely clear what mammographic density is biologically[5,6]. However, it has become clear that stromal fibrosis is a prominent feature in mammographically dense breasts[7-9] and an increased amount of epithe-

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lium and/or stroma are associated with more extensive percent mammographic density[10]. Moreover, dense breasts have higher level of collagen, and altered expression of stromal proteins[11,12].

The exact mechanisms and the role of stroma in causing cancer of epithelial cells have not yet been completely elucidated, mammographic density is associated with certain markers of epithelial growth, and most definitely with breast stroma. Indeed, epithelial and stromal cells, collagen, and fat, the tissue components that contribute to variations in mammographic density, are related to each other in several ways. Epithelial and stromal cells communicate with each other by means of paracrine growth factors[13]. Collagen is a product of stromal fibroblasts, and adipocytes develop from the differentiation of stromal preadipocytes[14]. Therefore, disorders of the cross-talk among epithelial cells and the surrounding stroma are deemed to participate in the aetiology of mammographic density and this interaction is known to be important in breast carcinogenesis[15]. Moreover, several studies point out that the average percentage of mammographic density in the population decreases with increasing age[16-19] and increasing age is also associated with a reduction in average amounts of stromal and epithelial tissues in the breast that are reflected in the percent mammographic density[20].

Percent mammographic density may, thus, reflect the cumulative exposure of breast stroma and epithelium to hormones and growth factors that stimulate cell division and changes in percent mammographic density with age may reflect changes in breast histology that are commonly referred to as involution. Furthermore, breast lesions including ductal carcinoma *in situ*, atypical hyperplasia, hyperplasia without atypia and columnar cell lesions are, to different degrees, associated with an increased risk of breast cancer and extensive percent mammographic density is associated with an increased risk of each of these lesions[6]. The breast density appears to have both a genetic component, but also a modifiable, non-genetic component[21,22]. Even hormonal mechanisms, the growth hormone-mediated release of free fatty acids from adipocytes, and an increase in the lipid substrate available for oxidative damage, might be involved in the pathogenesis[23].

Some studies show an increase of the breast density in post-menopausal users of hormone replacement therapy (HRT) and for this reason the antiestrogen tamoxifen is the favorite pharmacological treatment in the management of breast density. Tamoxifen treatment in postmenopausal women[24,25] and treatment with a gonadotrophin-releasing hormone agonist in premenopausal women[26], indeed, are associated with a reduction in the rate of mammographic density. These pharmacological treatments should be used only in selected cases because of their known adverse effects. As a matter of fact, breast density is still an enigmatic condition: its causes are poorly understood and are likely to be multifactorial. Current available therapies are inadequate and optimal strategy is still warranted.

Myo-inositol is a six-fold alcohol of cyclohexane, has been proved to modulate different pathways: inflammatory[27], metabolic[28], oxidative[29] and endocrine processes in a wide array of human diseases, including cancer[30]. Similarly, boswellic acid and betaine (three-methyl glycine)[31,32] both inhibit inflammation and exert protective effects on breast physiology[33,34].

Accordingly to these studies, in order to investigate new and safe therapeutic strategies to reduce breast density and to prevent the development of breast cancer, we hypothesized that a combination including myo-inositol, boswellic acid and betaine (Eumastós®) would be beneficial in breast density by displaying a pleiotropic effect on different pathways, targeting inflammatory, metabolic and endocrine processes altogether.

Patients and Methods

To investigate the therapeutic benefit of the experimental treatment we used a double-blind, randomized, placebo controlled, parallel group design. Between February 2014 and November 2015, 76 premenopausal women, aged between 22-51 years and with high breast density were included in the trial. Clinical and qualitative assessment of breast density was obtained by twice distinct opinions carried out by expert radiologists and was performed according to Boyd[7], subdividing patients into four main categories: 1) almost entirely fat, 2) scattered fibroglandular densities, 3) heterogeneously dense, 4) extremely dense.

Eligible criteria excluded: previous treatment for the breast or hormonal treatments during the last 4 months prior to the trial; patients affected by breast cancer, suffering from bloody nipple discharge, affected by pre-malignant lesions (carcinoma *in situ*), or other diseases were excluded.

Age, weight and clinical data were recorded by an experienced surgeon for each patient and are reported in Table I.

Table I. Baseline characteristics of premenopausal randomised patients who concluded the study.

Clinical data	Placebo-group	Experimental group
No. of patients	30	32
Age (mean, years) (SD)	39.1 (5.8)	38.7 (6.1)
Weight (mean, kg) (SD)	66.7 (5.6)	67.0 (3.4)
High breast density	22/30 (73%)	25/32 (78%)

In order to ensure a correct balance between groups, patients were randomized to treatment using a minimization procedure[39].

In the first group, patients received oral capsules (one capsule twice a day), containing a combination of vitamins (B2, B6, folic acid) and N-acetyl-cysteine; in the experimental arm, patients received oral capsules (one capsule twice a day), filled with the same control composition plus boswellic acid, betaine and myo-inositol.

The control and the experimental formula (Eumastós®) were kindly supplied from Lo.Li. Pharma srl., Rome, Italy and were designed to have an identical appearance (Table II).

The main outcome of the study was density reduction. Patients were requested not to change their diet during participation in the trial. Mammographic as well as ultrasound examination were performed at the baseline and after the treatment period (6 months).

Statistical Analysis

The few patients led us to adopt Fisher exact test for assessing significance instead of Chi-Square (cells with < 5 units). In addition to Fisher exact test significance, C.I: at 95% of the Odds Ratio is reported, the CI was estimated by means of Wald approximation. $p < 0.05$ was estimated statistically significant.

Results

Taken as a whole the compliance among the two groups was higher than expected, as the treatment was discontinued only in a few cases and for less than few days. Due to drop out, only 62 patients arrived at the last step of the study involving breast density analysis.

Table III reports the results obtained pertaining to the study groups (control and treatment).

Breast density

As expected for young women, mammary tissue density was increased in a relevant proportion of cases. Within the control group, 22 out of 30 patients showed grade four breast density (extremely dense) and 25/32 women in the experimental group were also affected by extremely dense breast tissue.

At the end of the trial, whereas no appreciable differences were found in the placebo group, an unexpected and significant decrease in breast density was recorded by mammography among patients of the experimental arm (60%). There-

Table II. Drug formula.

Component (mg)	Placebo-control group	IBAB
Myo-Inositol	-	200
Boswellic acid	-	50
Betaine	-	175
Vitamin B6	2.1	2.1
Folic acid	0.3	0.3
Vitamin B2	2.1	2.1
Vitamin B12	0.003	0.003
N-acetylcysteine	100	100
Posology	1 capsule twice a day	1 capsule twice a day

Table III. Number of patients with high breast density and breast density reduction in the two groups. OR (95% Confidence Interval) 2.46<15<118.3; *p*-values are estimated by Fisher exact test vs baseline.

	High breast density (n)		Breast density reduction (%)	*p*-value
	Pre-treatment	Post-treatment		
Placebo group	22	20	9.1%	ns
Experimental group	25	10	60%	0.001

fore, breast density reduction was significantly more marked in experimental arm ($p < 0.001$, Table III).

It is worth nothing that among those patients (15 responding patients out of 25 showing high breast density), reduction in tissue compactness was also associated to a significant pain reduction in almost all patients (13 out of 15, data not shown).

Adverse effects

Overall no significant adverse effects were recorded in both arms. Only one case in the experimental arm experienced transient mild diarrhoea.

Discussion

Data presented herein suggest that women showing high breast density, experience a significant clinical benefit when treated with a balanced composition including boswellic acid, betaine and myo-inositol (Eumastós®). A reduction in breast density was achieved in a relevant portion of patients enrolled in the experimental arm: differences in response rate between control and the experimental group showed to be very significant, indeed. Keeping in mind that increased breast density is deemed to be a pivotal risk factor for breast cancer[35] – being related to high tissue stiffness and augmented remodelling rate – reducing the mammary compactness by means of a 'simple', natural remedy, may bring about very relevant clinical outcomes.

In order to prevent breast cancer, there is considerable debate about the choice of the best agent for initial management of mammographic breast density[36-38]. Despite hormonal-based treatment have provided consistent benefit in a large proportion of patients, these drugs are difficult easy to handle for prolonged period of time. Consequently, the search for more manageable and safer treatment options prompted many clinicians to investigate different alternatives.

Several vitamins and antioxidants have been evaluated as support in the management and prevention of breast diseases. Among many formulations, those including folate intake, vitamin B1, B6, B12 and antioxidants, such as N-acetylcysteine, have yielded some good results[39-43] and to date, vitamins supplementation is usually recommended by general practitioners.

By hypothesizing a synergy in between three natural active compounds – boswellic acid, betaine and myo-inositol – sharing anti-inflammatory and endocrine-modulating activities, we have studied their combined effectiveness in a pilot, randomised trial.

Preliminary data collected herewith support the starting assumptions, that the association comprising boswellic acid, betaine and myo-inositol significantly reduces mammary density in a relevant percentage of patients, without any relevant side effects. Additionally, that formula ameliorates other symptoms, like anxiety and menstrual discomfort.

These effects are likely to be ascribed to the pleiotropic mechanism of action exerted by boswellia, betaine and myo-inositol on several metabolic, inflammatory as well as endocrine pathways. In particular the anti-inflammatory activity of Boswellia is well known and this property has been attributed to its ability in regulating immune cytokine production and leukocyte infiltration[44,45]. Indeed the acetyl-keto-β-boswellic acid (AKBA), a triterpenoid isolated from boswellia, is able to act as 5-lipoxygenase inhibitor[46,47]. The boswellia has also been proposed to provide antineoplastic through its anti-proliferative and proapoptotic properties in different human cancer cells[48,49]. Experimental models showed that boswellic acid is able to inhibit cell growth and to induce apoptosis in liver[50], colon[51] and prostate cancer[52]. Moreover, a study on breast cancer cells lines point out the ability of

boswellia to modulate the expression of signalling molecules and cell cycle regulators such as the caspase-3 in the MDA-MB-231 breast cancer cells, and the phosphorylated levels of Akt (Ser473) and Erk1/2 (Thr202/Tyr204) in MCF7 cells. It is involved also in down-regulation of the expression of cyclin D1, a crucial cell cycle regulator involved in cancer development and progression[53].

Myo-inositol showed to prevent pulmonary fibrosis after asbestos or inflammatory injury[54], to inhibit chronic colon inflammation, likely by modulating the redox balance[55]. In addition, myo-inositol and boswellia, may contrast inflammation-induced fibrosis by modulating TGF-β activity. TGF-β, in particular the TGF-β1 isoform, is a potent pro-fibrogenic agent inducing collagen synthesis and regulating the balance between matrix-degrading metalloproteinases and their inhibitors[56,57], thus, resulting a prominent factor in orchestrating the cross-talk among epithelial cells and their microenvironment[58]. Myo-inositol significantly modulates the expression of genes encoding TGF-βs and their receptors, and by that way it exerts immune-regulatory effects on colonic epithelium under inflammatory conditions or during microbe-induced infection/inflammation in order to maintain the colonic mucosa in a non-inflammatory state or to counteract infection[59,60]. TGF-β down-regulation has been observed in breast diseases[61], such breast fibrosis is usually recorded as an increase of breast density during mammographic examination. Modulation of these important biological activities by myo-inositol and boswellia may improve the breast density. In addition, myo-inositol exerts a modulating activity on cell metabolism, by improving glucose uptake and normalizing lipid metabolism[62].

Therefore, it could be hypothesized that Myo-inositol may improve the clinic-pathological features of breast compactness by interfering with tissue metabolism at local and systemic level. In fact, as demonstrated by a compelling body of scientific data, Myo-inositol improves metabolic and hormonal pattern, being normally altered in PCOS patients[63,64]. In fact, Myo-inositol restore insulin sensitivity, counteract hyperandrogenism and modulates oestrogen and FSH activity at ovary level[65,66].

At last betaine, a nutrient involved in one-carbon metabolism and consequently in methylation of DNA, influences gene stability, expression and nucleotide synthesis and it intake could be useful in the prevention of breast cancer development[67,68]. Based on their mechanisms of action, we speculate that the contribute of all these substances in the different biological pathways may explain the positive effect on breast density.

Conclusions

Women showing high breast density, experience a significant clinical benefit when treated with a balanced composition including boswellic acid, betaine and myo-inositol. Undoubtedly, our study suffers from limitations and our main findings should be confirmed by a large survey, namely by evaluating how long should last the clinical response and how relevant could be the relapse rate. Yet, data reported herewith preliminarly demonstrated that the proposed treatment may ensure a high response rate without side-effects, thus making it a reliable option for prolonged period of mammographic density treatment.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Ursin G, Qureshi SA. Mammographic density – a useful biomarker for breast cancer risk in epidemiologic studies. Norsk Epidemiologi 2009; 19: 59-68.
2) Boyd NF, Guo H, Martin LJ, Sun L, Stone J, Fishell E, Jong RA, Hislop G, Chiarelli A, Minkin S, Yaffe MJ. Mammographic density and the risk and detection of breast cancer. N Engl J Med 2007; 356: 227-236.
3) Boyd NF, Martin LJ, Yaffe MJ, Minkin S. Mammographic density and breast cancer risk: current understanding and future prospects. Breast Cancer Res 2011; 13: 223.
4) Boyd NF, Martin LJ, Bronskill M, Yaffe MJ, Duric N, Minkin S. Breast tissue composition and susceptibility to breast cancer. J Natl Cancer Inst 2010; 102: 1224-1237.

5) Pang JMB, Byrne DJ, Takano EA, Jene N, Petelin L, McKinley J, Poliness C, Saunders C, Taylor D, Mitchell G, Fox SB. Breast tissue composition and immunophenotype and its relationship with mammographic density in women at high risk of breast cancer. PLoS One 2015; 10: e0128861.

6) Tice JA, O'Meara ES, Weaver DL, Vachon C, Ballard-Barbash R, Kerlikowske K. Benign breast disease, mammographic breast density, and the risk of breast cancer. J Natl Cancer Inst 2013; 105: 1043-1049.

7) Oza AM, Boyd NF. Mammographic parenchymal patterns: a marker of breast cancer risk. Epidemiol Rev 1993; 15: 196-208.

8) Fisher ER, Palekar A, Kim WS, Redmond C. The histopathology of mammographic patterns. Am J Clin Pathol 1978; 69: 421-426.

9) Arthur JE, Ellis IO, Flowers C, Roebuck E, Elston CW, Blamey RW. The relationship of "high risk" mammographic patterns to histological risk factors for development of cancer in the human breast. Br J Radiol 1990; 63: 845-849.

10) Hawes D, Downey S, Pearce CL, Bartow S, Wan P, Pike MC, Wu AH. Dense breast stromal tissue shows greatly increased concentration of breast epithelium but no increase in its proliferative activity. Breast Cancer Res 2006; 8: R24.

11) Guo YP, Martin LJ, Hanna W, Banerjee D, Miller N, Fishell E, Khokha R, Boyd NF. Growth factors and stromal matrix proteins associated with mammographic densities. Cancer Epidemiol Biomarkers Prev 2001; 10: 243-248.

12) Alowami S, Troup S, Al-Haddad S, Kirkpatrick I, Watson PH. Mammographic density is related to stroma and stromal proteoglycan expression. Breast Cancer Res 2003; 5: R129-135.

13) Hagios C, Lochter A, Bissell M. Tissue architecture: the ultimate regulator of epithelial function? Philos Trans R Soc Lond B Biol Sci 1998; 353: 857-870.

14) Zangani D, Darcy KM, Masso-Welch PA, Bellamy ES, Desole MS, Ip MM. Multiple differentiation pathways of rat mammary stromal cells in vitro: acquisition of a fibroblast, adipocyte or endothelial phenotype is dependent on hormonal and extracellular matrix stimulation. Differentiation 1999; 64: 91-101.

15) Barcellos-Hoff MH, Medina D. New highlights on stroma-epithelial interactions in breast cancer. Breast Cancer Res 2005; 7: 33-36.

16) Byrne C, Schairer C, Wolfe J, Parekh N, Salane M, Brinton LA, Hoover R, Haile R. Mammographic features and breast cancer risk: effects with time, age, and menopause status. J Natl Cancer Inst 1995; 87: 1622-1629.

17) Grove JS, Goodman MJ, Gilbert FI, Clyde D. Factors associated with breast structures in breast cancer patients. Cancer 1979; 43: 1895-1899.

18) Wolfe JN. Breast parenchymal patterns and their changes with age. Radiology 1976; 121(3 pt 1): 545-552.

19) Milanese TR, Hartmann LC, Sellers TA, Frost MH, Vierkant RA, Maloney SD, Pankratz VS, Degnim AC, Vachon CM, Reynolds CA, Thompson RA, Melton LJ 3rd, Goode EL, Visscher DW. Age-related lobular involution and risk of breast cancer. J Natl Cancer Inst 2006; 98: 1600-1607.

20) Li T, Sun L, Miller N, Nicklee T, Woo J, Hulse-Smith L, Tsao MS, Khokha R, Martin L, Boyd N. The association of measured breast tissue characteristics with mammographic density and other risk factors for breast cancer. Cancer Epidemiol Biomarkers Prev 2005; 14: 343-349.

21) Rudolph A, Fasching PA, Behrens S, Eilber U, Bolla MK, Wang Q, Thompson D, Czene K, Brand JS, Li J, Scott C, Pankratz VS, Brandt K, Hallberg E, Olson JE, Lee A, Beckmann MW, Ekici AB, Haeberle L, Maskarinec G, Le Marchand L, Schumacher F, Milne RL, Knight JA, Apicella C, Southey MC, Kapuscinski MK, Hopper JL, Andrulis IL, Giles GG, Haiman CA, Khaw KT, Luben R, Hall P, Pharoah PD, Couch FJ, Easton DF, Dos-Santos-Silva I, Vachon C, Chang-Claude J. A comprehensive evaluation of interaction between genetic variants and use of menopausal hormone therapy on mammographic density. Breast Cancer Res 2015; 17: 110.

22) Martin LJ, Boyd NF. Potential mechanisms of breast cancer risk associated with mammographic density: hypotheses based on epidemiological evidence. Breast Cancer Res 2008; 10: 201.

23) Nam SY, Lobie PE. The mechanism of effect of growth hormone on preadipocyte and adipocyte function. Obes Rev 2000; 1: 73-86.

24) Cuzick J, Warwick J, Pinney E, Duffy SW, Cawthorn S, Howell A, Forbes JF, Warren RM. Tamoxifen-induced reduction in mammographic density and breast cancer risk reduction: a nested case-control study. J Natl Cancer Inst 2011; 103: 744-752.

25) Cuzick J, Warwick J, Pinney E, Warren RM, Duffy SW. Tamoxifen and breast density in women at increased risk of breast cancer. J Natl Cancer Inst 2004; 96: 621-628.

26) Spicer DV, Ursin G, Parisky YR, Pearce JG, Shoupe D, Pike A, Pike MC. Changes in mammographic densities induced by a hormonal contraceptive designed to reduce breast cancer risk. J Natl Cancer Inst 1994; 86: 431-436.

27) Liao J, Seril DN, Yang AL, Lu GG, Yang GY. Inhibition of chronic ulcerative colitis associated adenocarcinoma development in mice by inositol compounds. Carcinogenesis 2007; 28: 446-454.

28) Giordano D, Corrado F, Santamaria A, Quattrone S, Pintaudi B, Di Benedetto A, D'Anna R. Effects of myo-inositol supplementation in postmenopausal women with metabolic syndrome: a perspective, randomized, placebo-controlled study. Menopause 2011; 18: 102-104.

29) Donà G, Sabbadin C, Fiore C, Bragadin M, Giorgino FL, Ragazzi E, Clari G, Bordin L, Armanini D. Inositol administration reduces oxidative stress in erythrocytes of patients with polycystic ovary syndrome. Eur J Endocrinol 2012; 166: 703-710.

30) Shamsuddin AM. Anti-cancer function of phytic acid. Int J Food Sci Technol 2002; 37: 769-782.

31) Detopoulou P, Panagiotakos DB, Antonopoulou S, Pitsavos C, Stefanadis C. Dietary choline and betaine intakes in relation to concentrations of inflammatory markers in healthy adults: the ATTICA study. Am J Clin Nutr 2008; 87: 424-430.

32) Go EK, Jung KJ, Kim JY, Yu BP, Chung HY. Betaine suppresses proinflammatory signaling during aging: the involvement of nuclear factor-kappaB via nuclear factor-inducing kinase/IkappaB kinase and mitogen-activated protein kinases. J Gerontol 2005; 60: 1252-1264.

33) Cho E, Holmes MD, Hankinson SE, Willett WC. Choline and betaine intake and risk of breast cancer among post-menopausal women. Br J Cancer 2010; 102: 489-494.

34) Ammon HP. Boswellic acids in chronic inflammatory diseases. Planta Med 2006; 72: 1100-1116.

35) Boyd NF, Guo H, Martin LJ, Sun L, Stone J, Fishell E, Jong RA, Hislop G, Chiarelli A, Minkin S, Yaffe MJ. Mammographic density and the risk and detection of breast cancer. N Engl J Med 2007; 356: 227-236.

36) Greendale GA, Reboussin BA, Slone S, Wasilauskus C, Pike MC, Ursin G. Postmenopausal hormone therapy and change in mammographic density. J Natl Cancer Inst 2003; 95: 30-37.

37) Stuedal A, Ma H, Bjorndal H, Ursin G. Postmenopausal hormone therapy with estradiol and norethisterone acetate and mammographic density: findings from a cross-sectional study among Norwegian women. Climacteric 2009; 12: 248-258.

38) Cuzick J, Powles T, Veronesi U, Forbes J, Edwards R, Ashley S, Boyle P. Overview of the main outcomes in breast-cancer prevention trials. Lancet 2003; 361: 296-300.

39) Graham S, Hellmann R, Marshall J, Freudenheim J, Vena J, Swanson M, Zielezny M, Nemoto T, Stubbe N, Raimondo T. Nutritional epidemiology of postmenopausal breast cancer in western New York. Am J Epidemiol 1991; 134: 552-566.

40) Lajous M, Lazcano-Ponce E, Hernandez-Avila M, Willett W, Romieu I. Folate, vitamin B(6), and vitamin B(12) intake and the risk of breast cancer among Mexican women. Cancer Epidemiol Biomarkers Prev 2006; 15: 443-448.

41) De Batlle J, Ferrari P, Chajes V, Park JY, Slimani N, McKenzie F, Overvad K, Roswall N, Tjønneland A, Boutron-Ruault MC, Clavel-Chapelon F, Fagherazzi G, Katzke V, Kaaks R, Bergmann MM, Trichopoulou A, Lagiou P, Trichopoulos D, Palli D, Sieri S, Panico S, Tumino R, Vineis P, Bueno-de-Mesquita HB, Peeters PH, Hjartåker A, Engeset D, Weiderpass E, Sánchez S, Travier N, Sánchez MJ, Amiano P, Chirlaque MD, Barricarte Gurrea A, Khaw KT, Key TJ, Bradbury KE, Ericson U, Sonestedt E, Van Guelpen B, Schneede J, Riboli E, Romieu I. Dietary folate intake and breast cancer risk: European prospective investigation into cancer and nutrition. J Natl Cancer Inst 2014; 107: 367.

42) Vachon CM, Kushi LH, Cerhan JR, Kuni CC, Sellers TA. Association of diet and mammographic breast density in the Minnesota breast cancer family cohort. Cancer Epidemiol Biomarkers Prev 2000; 9: 151-160.

43) Venugopal D, Zahid M, Mailander P, Meza JL, Rogan EG, Cavalieri EL, Chakravarti D. Reduction of estrogen-induced transformation of mouse mammary epithelial cells by N-acetylcysteine. J Steroid Biochem Mol Biol 2008; 109: 22-30.

44) Abdel-Tawab M, Werz O, Schubert-Zsilavecz M. Boswellia serrata: an overall assessment of in vitro, preclinical, pharmacokinetic and clinical data. Clin Pharmacokinet 2011; 50: 349-369.

45) Ammon HP. Modulation of the immune system by Boswellia serrata extracts and boswellic acids. Phytomedicine 2010; 17: 862-867.

46) Ammon HP. Boswellic acids in chronic inflammatory diseases. Planta Med 2006; 72: 1100-1116.

47) Poeckel D, Werz O. Boswellic acids: biological actions and molecular targets. Curr Med Chem 2006; 13: 3359-3369.

48) Yadav VR, Prasad S, Sung B, Gelovani JG, Guha S, Krishnan S, Aggarwal BB. Boswellic acid inhibits growth and metastasis of human colorectal cancer in orthotopic mouse model by downregulating inflammatory, proliferative, invasive, and angiogenic biomarkers. Int J Cancer 2012; 130: 2176-2184.

49) Tolga Eichhorn T, Greten HJ, Thomas Efferth T. Molecular determinants of the response of tumor cells to boswellic acids. Pharmaceuticals (Basel) 2011; 4: 1171-1182.

50) Liu JJ, Nilsson A, Oredsson S, Badmaev V, Duan RD. Keto- and acetyl-keto-boswellic acids inhibit proliferation and induce apoptosis in Hep G2 cells via acaspase-8 dependent pathway. Int J Mol Med 2002; 10: 501-505.

51) Liu JJ, Nilsson A, Oredsson S, Badmaev V, Zhao WZ, Duan RD. Boswellic acids trigger apoptosis via a pathway dependent on caspase-8 activation but independent on Fas/Fas ligand interaction in colon cancer HT-29 cells. Carcinogenesis 2002; 23: 2087-2093.

52) Lu M, Xia L, Hua H, Jing Y. Acetyl-keto-beta-boswellic acid induces apoptosis through a death receptor 5-mediated pathway in prostate cancer cells. Cancer Res 2008; 68: 1180-1186.

53) Suhail MM, Wu W, Cao A, Mondalek FG, Fung KM, Shih PT, Fang YT, Woolley C, Young G, Lin HK. Boswellia sacra essential oil induces tumor cell-specific apoptosis and suppresses tumor aggressiveness in cultured human breast cancer cells. BMC Complement Altern Med 2011; 11: 129.

54) Kamp DW, Israbian VA, Yeldandi AV, Panos RJ, Graceffa P, Weitzman SA. Phytic acid, an iron chelator, attenuates pulmonary inflammation and fibrosis in rats after intratracheal instillation of asbestos. Toxicol Pathol 1995; 23: 689-695.

55) Sudheer Kumar M, Sridhar Reddy B, Kiran Babu S, Bhilegaonkar PM, Shirwaikar A, Unnikrishnan MK. Antiinflammatory and antiulcer activities of phytic acid in rats. Indian J Exp Biol 2004; 42: 179-185.

56) Di Sabatino A, Jackson CL, Pickard KM, Buckley M, Rovedatti L, Leakey NA, Picariello L, Cazzola P, Monteleone G, Tonelli F, Corazza GR, MacDonald TT, Pender SL. Transforming growth factor β signalling and matrix metalloproteinases in the mucosa overlying Crohn's disease strictures. Gut 2009; 58: 777-789.

57) Umar S, Umar K, Sarwar AH, Khan A, Ahmad N, Ahmad S, Katiyar CK, Husain SA, Khan HA. Boswellia serrata extract attenuates inflammatory mediators andoxidative stress in collagen induced arthritis. Phytomedicine 2014; 21: 847-856.

58) Kapral M, Wawszczyk J, Jurzak M, Hollek A, Weglarz L. The effect of inositol hexaphosphate on the expression of selected metalloproteinases and their tissue inhibitors in IL-1□-stimulated colon cancer cells. Int J Colorectal Dis 2012; 27: 1419-1428.

59) Weglarz L, Wawszczyk J, Orchel A, Jaworska-Kik M, Dzierzewicz ZL. Phytic acid modulates in vitro IL-8 and IL-6 release from colonic epithelial cells stimulated with LPS and IL-1beta. Dig Dis Sci 2007; 52: 93-102.

60) Wawszczyk J, Kapral M, Hollek A, Weglarz L. The effect of phytic acid on the expression of NF-kappaB, IL-6 and IL-8 in IL-1beta-stimulated human colonic epithelial cells. Acta Pol Pharm 2012; 69: 1313-1319.

61) Gobbi H, Dupont WD, Simpson JF, Plummer WD Jr, Schuyler PA, Olson SJ, Arteaga CL, Page DL. Transforming growth factor-beta and breast cancer risk in women with mammary epithelial hyperplasia. J Natl Cancer Inst 1999; 91: 2096-2101.

62) Onomi S, Okazaki Y, Katayama T. Effect of dietary level of phytic acid on hepatic and serum lipid status in rats fed a high-sucrose diet. Biosci Biotechnol Biochem 2004; 68: 1379-1381.

63) Genazzani AD, Lanzoni C, Ricchieri F, Jasonni VM. Myo-inositol administration positively affects hyperinsulinemia and hormonal parameters in overweight patients with polycystic ovary syndrome. Gynecol Endocrinol 2008; 24: 139-144.

64) Costantino D, Minozzi G, Minozzi E, Guaraldi C. Metabolic and hormonal effects of myo-inositol in women with polycystic ovary syndrome: a double-blind trial. Eur Rev Med Pharmacol Sci 2009; 13: 105-110.

65) Huang LC, Fonteles MC, Houston DB, Zhang C, Larner J. Chiroinositol deficiency and insulin resistance. III. Acute glycogenic and hypoglycemic effects of two inositol phosphoglycan insulin mediators in normal and streptozotocin-diabetic rats in vivo. Endocrinology 1993; 132: 652-657.

66) Orihuela PA, Parada-Bustamante A, Zuñiga LM, Croxatto HB. Inositol triphosphate participates in an oestradiol nongenomic signalling pathway involved in accelerated oviductal transport in cycling rats. J Endocrinol 2006; 188: 579-588.

67) Zhang CX, Pan MX, Li B, Wang L, Mo XF, Chen YM, Lin FY, Ho SC. Choline and betaine intake is inversely associated with breast cancer risk: a two-stage case-control study in China. Cancer Sci 2013; 104: 250-258.

68) Xu X, Gammon MD, Zeisel SH, Bradshaw PT, Wetmur JG, Teitelbaum SL, Neugut AI, Santella RM, Chen J. High intakes of choline and betaine reduce breast cancer mortality in a population-based study. FASEB J 2009; 23: 4022-4028.