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Effective combination therapies for preventing and treating highly prevalent human diseases: cancers, heart-failure, tuberculosis and malaria

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ABSTRACT: Methyl jasmonate has emerged as a tool for the selective activation of sarcoplasmic reticulum Ca^{2+}-ATPase in slow-twitch skeletal muscle and a regulator of calcium homeostasis in this tissue. An invention which provided the technology for the prevention of skeletal muscle degeneration commonly caused by malnutrition, cancer, tuberculosis and the acquired immune deficiency syndrome (AIDS), has been patented (US Patents 6,465,021 of October 15, 2002 and 6,887,499 of May 3, 2005). The second object of the invention is to provide a formulation for preventing the skeletal muscle wasting that does not adversely affect calcium homeostasis or induce additional oxidative stress of the muscle cells. The formulation includes at least one of the jasmonate family of stress hormones in an effective manner, at least one of the flavonoid antioxidants, and carnitine.

Since 2006 and after the release of the invention, there have been continuous positive support and provision of scientific evidence from numerous researchers, in various parts of the world, justifying the inclusion of each of the three components of the formulation. An emerging scenario suggests that inhibitors of 5-lipoxygenase (5-LOX) and cycloxygenase-2 (COX-2) could be useful in preventing and treating diseases such as cancer, heart failure and malaria.

Introduction

Certain disease states produce skeletal muscle wasting during the progression of the disease. In some cases, the drugs used in the treatment of these diseases also contribute to muscle wasting because they produce free radicals. Skeletal muscle degenerative diseases include malnutrition, cancer, tuberculosis and HIV/AIDS. It is usually the muscle wasting/degeneration accompanying treatment that hastens the death of patients suffering from these diseases. A formulation has been patented which holds the promise of extending the lives of the patients by reducing/slowing down the rate of skeletal muscle wasting (Bababunmi 2002a). Emerging reports in the literature also suggest that this formulation could be useful in the treatment of various types of cancer, notably prostate cancer (Yeruva *et al*., 2006; Lynch *et al*., 2007; Ezekwudo *et al*., 2007; Wang *et al*., 2008).

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Pulmonary Tuberculosis and HIV/AIDS

The current clinical research focus in our laboratory is on finding ways of arresting the muscle wasting associated with some diseases such as, malnutrition (kwashiorkor, marasmus), malaria, cancer, tuberculosis and HIV/AIDS (Bababunmi 2002b; Bababunmi and Bewaji, 2002; Salami and Oluboyo, 2002, 2003). At the University of Ilorin Teaching Hospital (UITH), Nigeria, we had earlier conducted a retrospective study to determine the prevalence of Pulmonary Tuberculosis (PTB) and seroprevalence of Human Immunodeficiency Virus (HIV) infection amongst PTB cases, from 1991 to 1999. The study was over a nine-year period. The annual distribution of all PTB and PTB/HIV co-infected cases were estimated, so was the annual distribution of all medical cases seen over the same period. A total of 104,240 medical cases were seen, out of which 9697 were confirmed PTB. This gives a prevalence rate of 9.2%. Their sex ratio was M:F 1.3:1 and about 81.6% of them were between 15-54 years of age. One hundred and eighty nine out of 1496 cases of PTB screened for HIV antibody were seropositive giving a seroprevalence rate of 12.6%. The annual distribution of PTB/HIV co-infection showed a rising trend from only one case in 1991 to 20 cases in 1999. This trend has continued to rise, as 114 patients had PTB/HIV co-infection within the last 4 years from 1st January to 1st December 2003 as against 189 patients in the previous nine year period.

PTB patients were managed on a 6 -months short course regimen of oral anti PTB drugs comprising intensive phase of 2 months of Rifampicin 10-20mg/kg, Isoniazid 5-10mg/kg, Ethambutol 15-25mg/kg and Pyrazinamide 35mg/kg. Then 4 months of Isoniazid and Rifampicin in the maintenance phase, or 9 months regimen of Isoniazid, Rifampicin and Ethambutol in the intensive phase and 7 months maintenance phase of Rifampicin and Isoniazid.

Patients that had PTB/HIV co-morbidity were in addition to anti- TB medications placed on the Federal Government-sponsored Highly Active Anti-Retroviral Therapy (HAART) The HIV status in these patients were determined by enzyme-linked immunosorbent assay (ELISA) HIV I and II kits based in the Haematology Department.

In a recent study, we had tried to look at indices for monitoring the nutritional status of our PTB patients. The objective was to evaluate the relative roles if urinary creatinine and serum albumin as biochemical markers for monitoring the nutritional status of PTB patients during treatment. Thirty-one diagnosed PTB patients were placed on six months short course regimen. Their weight, body mass index, serum albumin and 24-hour urinary creatinine excretion were determined before treatment, at the end of the 1st, 2nd, 4th,and 6th month of treatment. Subjecting the mean values of the weight, BMI and Urinary Creatinine excretion and serum albumin to Friedman test showed significant changes for all the four indices. Further analysis with paired student t-test of the pre-treatment values with end of 6th month values confirmed significant changes in the mean values of weight, BMI and serum albumin. Of these three indices serum albumin with chi-square value of 103.515 demonstrated the most significant changes, while the minimal change observed in urinary creatinine excretion could not be confirmed with paired t-test. We recommended serum (as a more sensitive index) for monitoring the nutrition of patients with pulmonary tuberculosis.

Inflammation and Cancer

The therapeutic roles of dual inhibitors of 5-LOX and COX-2 as potential drugs to treat inflammation and various types of cancer have been proposed (Martel-Pelletier *et al*., 2003; Horrillo *et al*., 2007; Tavolari *et al*., 2008; Bishayee and Khuda-Bukhsh, 2013). 5-LOX inhibitors include stress hormones such as methyl jasmonate and acetylsalicylate while COX-2 inhibitors include antioxidants such as ellagic acid and resveratrol. Fig. 1 shows the structures of common non-steroidal anti-inflammatory drugs (NSAIDs) some of which directly target COX-2, an enzyme responsible for inflammation and pain. The synthesis of prostaglandins involves cyclooxygenase-1(COX-1) and they are responsible for the maintenance and protection of the gastrointestinal tract. The well known NSAIDs differ in their relative specificities for COX-1 and COX-2. Aspirin and ibuprofen inhibit COX-2 and COX-1 while other NSAIDs appear to have partial COX-2 specificity, particularly meloxicam.

COX-2 has been linked to cancers and abnormal growth in the intestinal tract and COX inhibitor have also been shown to reduce the occurrence of cancers and pre-cancerous growth. COX-2 inhibitors have been studied in breast cancer with some beneficial results (Chow *et al*., 2005; Farooqui *et al*., 2007). The selective COX-2 inhibitor celecoxib exhibits both anti-inflammatory and analgesic properties. A number of studies listed in Table 1 have reported the anti-cancer effects of methyl jasmonate and COX-2 inhibitors and dual 5-LOX/COX-2 inhibitors.

Table 1: Drugs and compounds with anti-cancer properties.

Drug/Compound	Activities	Ref.
Licofelone	Dual COX/5-LOX inhibitor inducing apoptosis in HCA-7 colon cancer cells.	Tavolari *et al*., 2007
Aspirin	Non-selective COX inhibitor	Ganesh *et al*., 2012
Rofecoxib	Selective COX-2 inhibitor	Ganesh *et al*., 2012
Flavocoxid	Dual COX-2/5-LOX inhibitor which reduces prostate weight and hyperplasia.	Altavilla *et al*., 2012
SC-236	Selective COX-2 inhibitor which protects against liver inflammation and fibrosis.	Horrillo *et al*., 2007
Methyl jasmonate	Amelioration of muscle wasting induced by malnutrition or disease; induction of apoptosis in human prostate adenocarcinoma cell line (PC-3)	Bababunmi 2002a,b; Flescher, 2005; Rotem *et al*., 2003, 2005; Ezekwudo *et al*., 2008; Wang *et al*., 2008.
Celecoxib	Selective inhibitor of COX-2 used for the treatment of rheumatoid arthritis; also exhibits anticancer activities including induction of apoptosis in human cancer cell lines.	Sadeghi-Aliabadi *et al*., 2013.

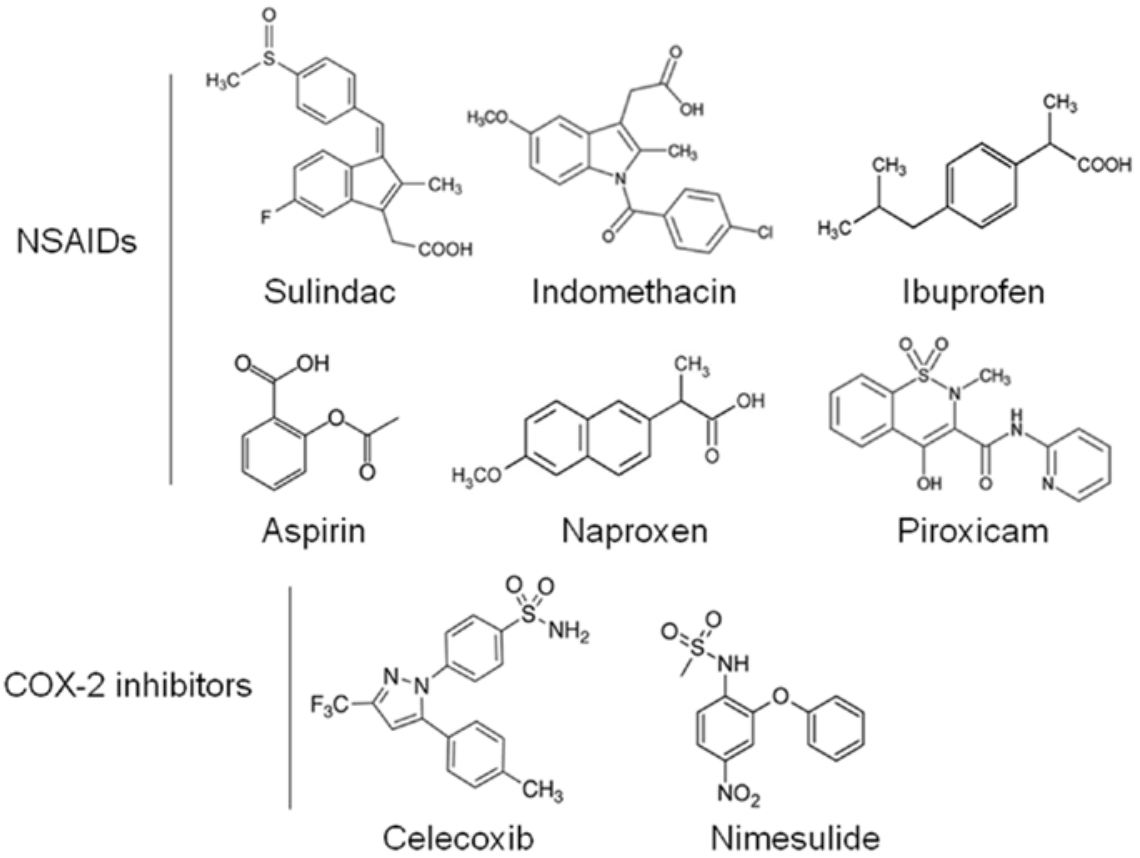

Fig. 1. Chemical structures of common NSAIDs and selective COX-2 inhibitors (Martel-Pelletier *et al*. 2003).

Fig. 2 also shows the pathway for the metabolism of arachidonic acid and the enzymes involed in the inflammatory process. Inhibition of some of these enzymes has now been shown to produce anti-cancer effects.

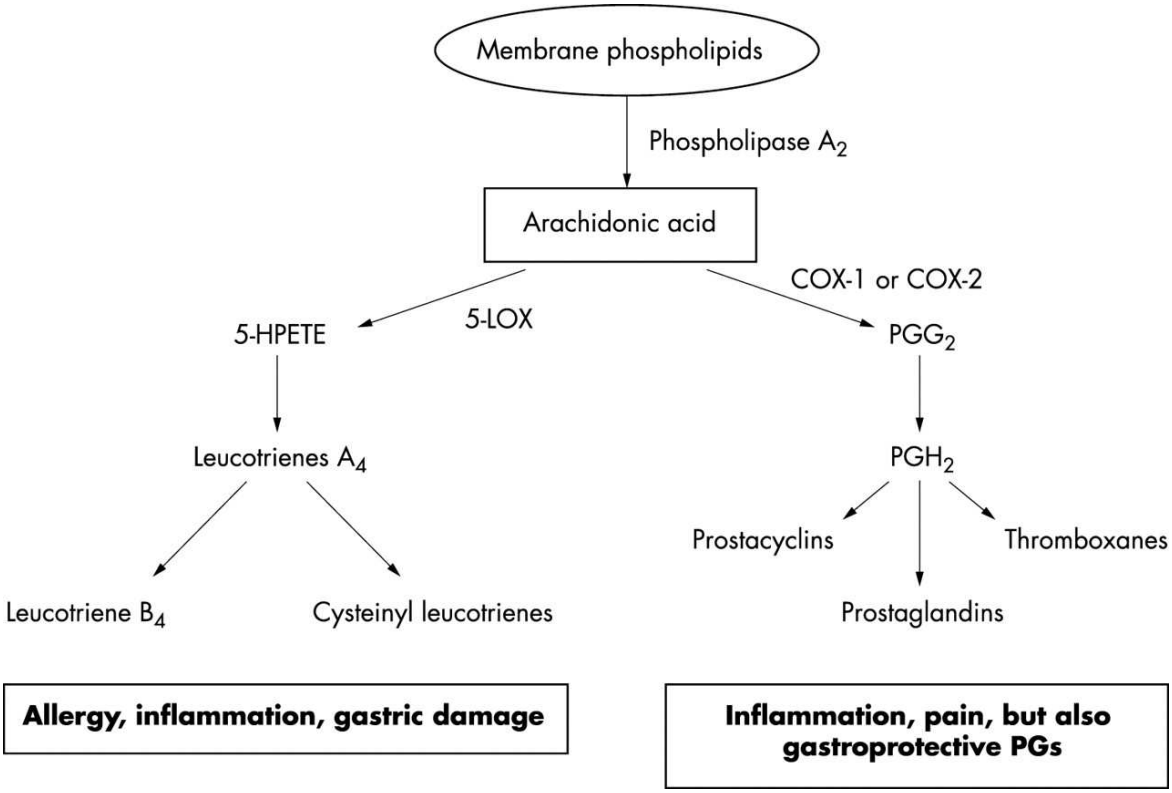

Fig. 2: Products and enzymes of arachidonic acid metabolism involved in the inflammatory process. (Martel-Pelletier *et al*. 2003)

Concluding Remarks

Some dietary phytochemicals, notably jasmonates, are emerging as tools that could be used as supplements in the treatment of muscle wasting induced by malnutrition and some diseases such a malaria, heart failure, tuberculosis, AIDS and various types of cancers. Recent reports in the literature also suggest that dual 5-LOX/COX-2 inhibitors possess anti-cancer properties which could be useful for the development of drugs for the prevention and treatment of various types of cancers.

References

Altavilla, D.; Minutolu, L.; Polito, F.; Irrera, N.; Arena, S.; Magno, C.; Rinaldi, M.; Burnett, B. P.; Squadrito, F. and Bitto, A. (2012) Effects of flavocoxid, a dual inhibitor of COX and 5-lipoxygenase enzymes, on benign prostatic hyperplasis. Br. J. Pharmacol. 167(1), 95 – 108.

Bababunmi, E. A. (2002a) Formulation and methods for treating skeletal muscle degeneration caused by malnutrition and disease. United States Patent No. US 006465021B2.

Bababunmi, E. A. (2002b) Skeletal muscle degeneration induced by malnutrition and disease: HIV/AIDS, Cancer, Tuberculosis and Malaria. Biokemistri 12(3), 143 – 146.

Bababunmi, E. A. and Bewaji, C. O. (2002) Oxidative stress and antioxidant therapy in wasting conditions associated with malnutrition, HIV/AIDS, tuberculosis and malaria. Biokemistri 12(3), 135 – 139.

Bishayee, K. and Khuda-Bukhsh, A. R. (2013) 5-Lipoxygenase antagonist therapy: A new approach towards targeted cancer chemotherapy. Acta Biochimica et Biophisica Sinica 45(9), 709 – 719.

Chow, L. W.; Loo, W. T. and Toi, M. (2005) Current directions for COX-2 inhibition in breast cancer. Biomed. Pharmacother. 59, 281 – 284.

Ezekwudo, D. E.; Wang, R. C. and Elegbede, J. A. (2007) Methyl jasmonate induced apoptosis in human prostate carcinoma cells via 5-lipoxygenase dependent pathway. Journal of Experimental Therapeutics and Oncology 6(4), 267 – 277.

Ezekwudo, D.; Shashidharamurthy, R.; Devineni, D.; Bozeman, E.; Palaniappan, R. and Selvaraj, P. (2008) Inhibition of expression of anti-apoptotic protein Bcl-2 and induction of cell death in radioresistant human prostate adenocarcinoma cell line (PC-3) by methyl jasmonate. Cancer Letters 270, 277 – 285.

Farooqui, M.; Li., Y.; Rogers, T. *et al*. (2007) COX-2 inhbibitor celecoxib prevents chronic morphine-induced promotion of angiogenesis, tumour growth, metastasis and mortality, without compromising analgesia. British Journal of Cancer 97(11), 1523 – 1531.

Flescher, E. (2005) Jasmonates: a new family of anti-cancer agents. Anticancer Drugs **16**, 911 – 916.

Ganesh, R.; Marks, D. J.; Sales, K.; Winslet, M. C. and Seifalian, A. M. (2012) Cyclooxygenase/lipoxygenase shunting lowers the anti-cancer effect of cyclooxygenase-2 inhibition in colorectal cancer cells. World J. Surg. Oncol. 10, 200.

Horrillo, R.; Planaguma, A.; Gonzalez-Periz, Ferre, N.; Titos, E.; Miquel, R.; Lopez-Parra, M.; Masferrer, J. L.; Arroyo, V. and Claria, J. (2007) Comparative protection against liver inflammation and fibrosis by a selective cyclooxygenase-2 inhibitor and a nonredoc-type 5-lipoxygenase inhibitor. Journal of Pharmacology and Experimental Therapeutics 323(3), 778 – 786.

Lynch, G. S.; Schertzer, J. D. and Ryall, J. G. (2007) Therapeutic approaches for muscle wasting disorders. Pharmacology and Therapeutics **113**, 461 – 487.

Martel-Pelletier, J.; Lajeunesse, D.; Reboul, P. and Pelletier, J-P. (2003) Therapeutic role of dual inhibitors of 5-LOX and COX, selective and non-selective non-steroidal anti-inflammatory drugs. Annals of Rheumatic Diseases 62, 501 – 509.

Rotem R, Fingrut O, Moskovitz J, Flescher E. (2003) The anticancer agent methyl jasmonate induces activation of stress-regulated c-Jun N-terminal kinase and p38 protein kinase in human lymphoid cells. Leukemia **17**, 2230–4.

Rotem, R.; Heyfets, A.; Fingrut, O.; Blickstein, D.; Shaklai, M. and Flescher, E. (2005) Jasmonates: Novel anticancer agents acting directly and selectively on human cancer cell mitochondria. Cancer Research 65, 1984.

Sadeghi-Aliabadi, H.; Aliasghariuo, M. Fatahi, A.; Mirian, M. and Ghannadian, M. (2013) In vitro cytotoxic evaluation of some synthesized COX-2 inhibitor derivatives against a panel of human cancer cell lines. Research in Pharmaceutical Sciences 8(4), 298 – 303.

Salami, A. K. and Oluboyo, P. O. (2002) Hospital prevalence of pulmonary tuberculosis and co-infection with human immunodeficiency virus in Ilorin: A review of nine years (1991 – 1999). West Afr. J. Med. 21(1), 24 – 27.

Salami, A. K. and Oluboyo, P. O. (2003) Management outcome of pulmonary tuberculosis: A nine year review in Ilorin. West Afr. J. Med. 22(2), 111 – 114.

Tavolari, S.; Bonafe, M., Marini, M.; Ferreri, C.; Bartolini, G.; Brighenti, E.; Manara, S.; Tomasi, V.; Laufer, S. and Guarnieri, T. (2007) Licofelone, a dual COX/5-LOX inhibitor, induces apoptosis in HCA-7 colon cancer cells theough the mitochondrial pathway independently from its ability to affect the arachidonic acid cascade. Carcinogenesis 29(2), 171 – 180.

Wang, S. Y.; Bowman, L. and Ding, M. (2008) Methyl jasmonate enhances antioxidant activity and flavonoid content in blackberries (*Rubus* sp.) and promotes antiproliferation of human cancer cells. Food Chemistry 107(3), 1261 – 1269.

Yeruva, L.; Pierre, K. J.; Carper, S. W.; Elegbede, J. A.; Toy, B. J. and Wang, R. C. (2006) Jasmonates induce apoptosis and cell cycle arrest in non-small cell lung cancer lines. Exp. Lung Res. **32**(10), 499 – 516.