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Review

Diabetes as a risk factor to cancer: Functional role of fermented papaya preparation as phytonutraceutical adjunct in the treatment of diabetes and cancer

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ABSTRACT

Oncologists and diabetologists quote scientific data from epidemiological and in vitro studies to show that high levels of insulin and glucose, in combination with oxidative stress and chronic inflammation, can heighten the risk of developing cancer amongst patients with diabetes. Although the cancers that have been consistently associated with type 2 diabetes include pancreatic, colorectal, breast and liver cancer, the preponderance of the disease risk factors such as obesity, inflammation, hyperglycemia, hyperinsulinaemia (as a result of insulin resistance and oxidative β-cell damage) and the indirect influence of anti-diabetic medications are increasingly being defined. Fermented papaya preparation (FPP) has defined antioxidant and immune-modulating potentials. The ability of FPP influence signaling cascades associated with cell growth and survival presents a rational for chemopreventive adjunct that can be used in combination with traditional redox based therapies that target oxidative stress in the cancer micro environment. It is further suggested that the demonstrated efficacy FPP to control blood glucose, excessive inflammation and modulate free radical-induced oxidative damage which are triggers of liver, bladder, breast and prostate cancers in type 2 diabetics, may favorably mitigate the side effects of ensuing diabetes and cancer therapy. What remains paramount is early cancer detection and early determination of propensity risks for diabetes. The education of patients, proper dietary management and compliance with therapeutic regime directed at cancer and diabetes encapsulate challenges of global magnitude.

Contents

Abbreviations: T2DM, Type 2 diabetes mellitus; IGF-1, insulin-like growth factor; IGFBP-3, insulin-like growth factor binding protein-3; PI3K, phosphatidyl inositol 3-kinase; AKT, protein kinase B; MAPK, mitogen-activated protein kinase; ISO, International Organization for Standardization; TNF-α, tumor necrosis factor-alpha; IL, interleukin; IFN-γ, interferon-gamma; FPP, fermented papaya preparation; ROS, reactive oxygen species; As_2O_3, arsenic trioxide; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; ALT, alanine aminotransferase; H_2O_2, hydrogen peroxide; MC-PROXYL, 3-methoxycarbonyl-2,2,5,5-tetramethyl-pyrrolidine-1-oxyl; Fe-NTA, ferric nitrilotriacetate complex; HCV, hepatitis C virus; PC12, pheochromocytoma; CCl_4, carbon tetrachloride; AST, aspartate aminotransferase; GPx, glutathione peroxidase; PPARγ, peroxisome proliferator activated receptor gamma; AMPK, adenine monophosphate-activated protein kinase; NO, nitric oxide.

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1. Introduction

Although cancer mortality and morbidity has continued to reach staggering proportions in low and middle-income countries, its clinical therapies have included surgery, chemotherapy, radiation and immunosuppression that are often viewed as costly or inaccessible urging the imperative need for novel intervention strategies. Type 2 diabetes mellitus is a disorder in which hyperglycemia and hyperinsulinemia coexist as a result of gradual β-cell failure and insulin resistance [1]. Prolonged exposure of organs to elevated glucose levels (which is usually decades long for some individuals) may be a major contributing factor as to why diabetes and cancer incidence are more prevalent in middle aged adults [2,3]. Large scale cohort studies clearly demonstrate a consistent association between high blood glucose and cancer incidence and mortality [4]. Experimental studies exploring the responsiveness of tumor growth to exogenous glucose are generally in agreement that hyperglycemic conditions indeed favor cell growth, anti-apoptosis, increased cell motility and boost invasiveness [5]. The promotion of early-stage breast and prostate tumor growth under the influence hyperinsulinemia is frequently related to the shared involvement of IGF-1 and IGFBP-3 receptors in phosphatidyl inositol 3-kinase (PI3K)/AKT and mitogen-activated protein kinase (MAPK) signaling pathways [6–8]. Insulin resistance may also trigger cancer development via other mechanisms such as: over expression of estrogen, interleukin-6, leptin, TNF-α and plasminogen activator inhibitor-1 [9]. This theoretically suggests that normalization of glucose levels through insulin therapy could possibly constrain cancer progression.

The belief "let food be thy medicine, and let thy medicine be thy food" as articulated by Hippocrates several thousand years ago is receiving much interest, particularly the health enhancing role of functional foods [10]. The market for products of natural origin and formulated foods that are potentially beneficial to cancer treatment extend to grains, marine organisms and spices whose health benefits surpass that of its traditional nutritional content. There is a shifting trend toward personalized medication and functional foods that are traditionally chosen as a means of enhancing the health status and emotional wellbeing. There remains a limited access to medicinal drugs and increasing belief in alternative therapy by those seeking relief to symptoms associated with chronic illness [11,12]. The therapeutic role of plant-based dietary antioxidants has been underestimated in the past, but accumulating evidence from epidemiological studies clearly underlines an inverse association between the consumption of diets high in fresh fruits and vegetables and the occurrence of diabetes and cancer [13–15]. The outcome of such studies must then be translated into effective feasible treatment regimes that can be easily implemented to curb the progression of diabetes into cancer. What is paramount is early cancer detection and education of the proper dietary management of cancer and diabetes both contexts encapsulate the challenges of global magnitude.

2. Targeting cancer through the modulation of inflammation and oxidative stress: potential role for FPP

Fermented papaya preparation is an ISO 9002 and 14,001 certified dietary supplement made from the yeast fermentation of non-genetically modified *Carica papaya* using a biotechnological process that strictly adheres to international quality control regulations. Although the general composition of FPP has been ascertained by the Japan Food Research Laboratories, the appearance of novel oligosaccharides formed during the bio fermentation process has enhanced its dietary composition and given FPP its unique properties. FPP is probably the only dietary supplement to be extensively documented for its astounding free radical scavenging capability, modulation of endogenous phase II antioxidant enzymes (e.g. superoxide dismutase, catalase, glutathione peroxidase, therodoxin, xanthine oxidase) and simultaneous boosting of the overall natural defense mechanisms of the immune system (Fig. 1). The functional activities of FPP have been found to remain unaffected despite subjection to harsh storage conditions, highlighting FPP to be an actively stable and highly reliable dietary supplement [16]. Oxidative stress and inflammation mechanisms play pivotal roles in the pathophysiological of cancer and diabetes [17,18] as illustrated in Fig. 2. ROS have been shown to be carcinogenic and exert deleterious effects through redox imbalance and modulation of gene expression. Excessive free radicals not only direct damage toward cellular lipids and DNA but also participate in post-translational modifications of proteins or enzymes involved in carcinogenesis (e.g. activate oncogene products, angiogenesis and telomerases, inactivate DNA repair gene such as hoGG-1, tumor-suppressor proteins such as p53 and proapoptotic enzymes such as caspases) [19,20]. The scheme in Fig. 2 is illustrative of current thoughts on the mechanisms applicable. Whilst modest amounts of ROS do trigger pancreatic β-cell degranulation, tumor cell proliferation, invasion and survival [21,22], the effects of free radicals cannot be entirely regarded as a detrimental phenomenon as they also form an integral component of basic cell regulation and signaling pathways [23,24]. Levels of ROS that are above cellular tolerance can suppress tumor progression-forming the basis of most chemotherapeutic and radiotherapeutic agents, a paradox that presents a great challenge for the development of anti-cancer therapies exploiting ROS-induced oxidative stress [25].

It is possible that cancer cells may develop some form of resistance during persistent ROS attack, rendering them more aggressive and resistant to chemical eradication. For example: continuous exposure of bladder cancer cells to arsenic trioxide (As_2O_3) resulted in cancerous cells surmounting its genotoxic effects [25]. It was found that the influence of As_2O_3 enhanced the activation of cell's intrinsic antioxidant system and promoted the expression of cell survival proteins (e.g. reduced glutathione) – a chain reaction involving transcription factors [26]. The concept of ROS dependent mitogenic and anti-apoptosis signaling pathways represents a specific vulnerability that can be selectively targeted by antioxidants, representing a novel class of potential agents that could effectively eliminate cancer cells. Novel bioactive components including benzyl glucosinolate have been identified in an aqueous extract of papaya [27,28] and these exhibit anti-growth activity on several tumor cell lines. Li et al. [28] indicated that the pulp has more benzyl glucosinolates before the maturation of papaya and that this will be nearly all stored in the seed after the fruit has been matured. The reader is referred to the review paper of Nguyen et al. [29] which summarizes the results of extract-based or specific compound-based investigations and emphasizes the aspects that warrant future research to explore the bioactives in *C. papaya* for their anticancer activities. Indeed fermented papaya preparation

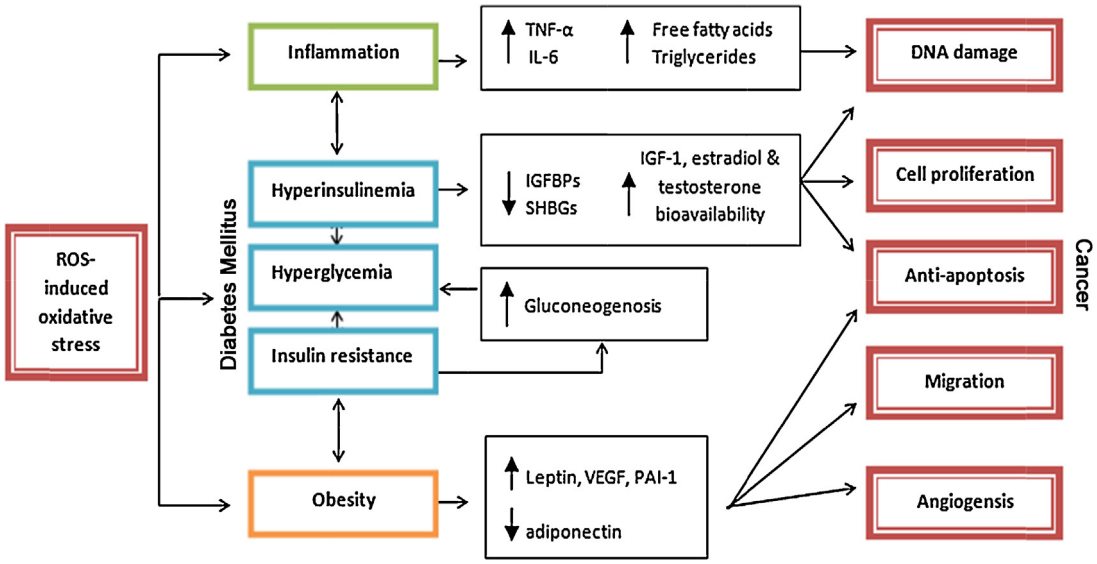

Fig. 1. A multidimensional model of cancer development which suggests ROS-triggered insulin resistance and inflammation as driving forces behind cancer: reactive oxygen species (ROS) are involved in the development of diabetes and can trigger the onset of inflammation and obesity-major modulators of cancer. ROS and hyperinsulinemia may promote cancer via the abnormal stimulation of multiple cellular signaling cascades. Reduced hepatic production of insulin-like growth factor binding proteins (IGFBPs) can dictate tumor growth and exert an anti-apoptotic effect by targeting transcriptions factors and tumor suppressor genes, likewise reduced sex-hormone binding globulins (SHBGs) influence the bioavailability of estrogen-increasing the risk of breast cancer in diabetics (adapted from [9]). TNF-α: tumor necrosis factor α; IL-6: interleukin-6; ROS: reactive oxygen species; SHBG: sex hormone-binding globulin; IGF-I: insulin-like growth factor I; PAI-1: plasminogen activator inhibitor-1; IGFBPs IGF-I binding proteins; VEGF, vascular endothelial growth factor.

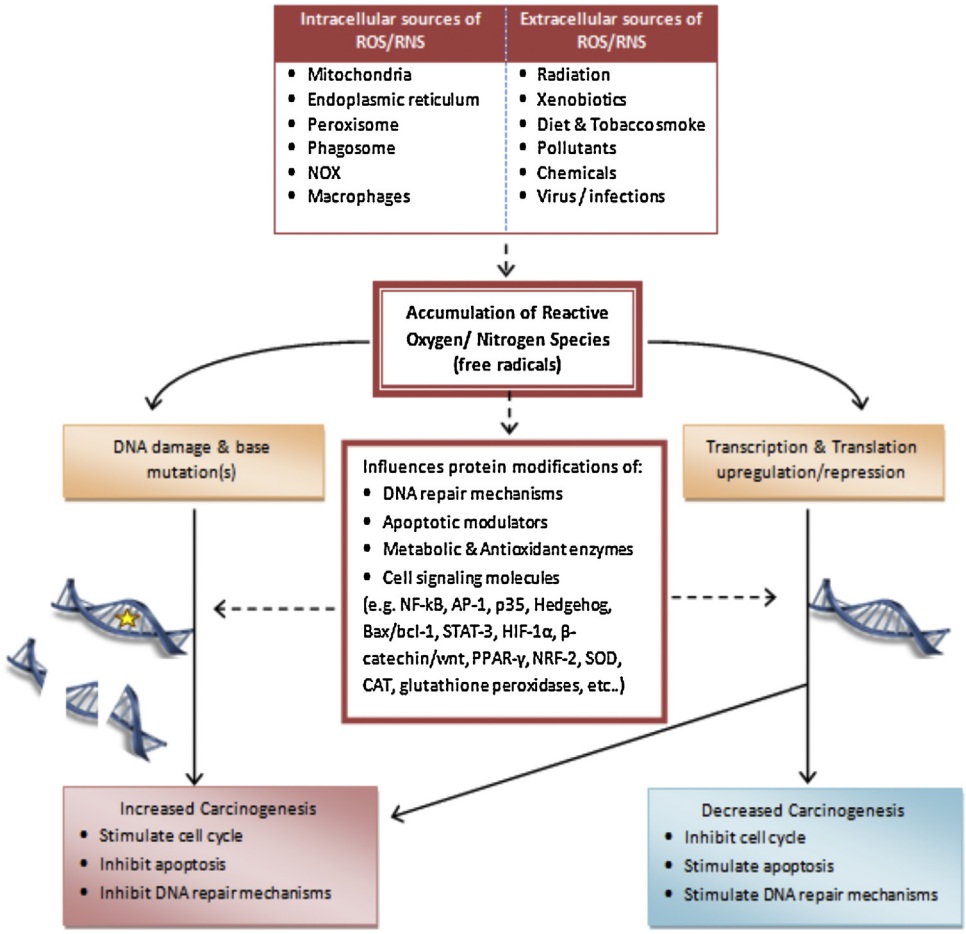

Fig. 2. Prolonged accumulation of free radicals can dictate many cellular processes involved in carcinogenesis. Free radicals not only attack DNA but also influence cancer-related suppressor genes and transcription factors involved in cell proliferation, apoptosis and DNA repair mechanisms.

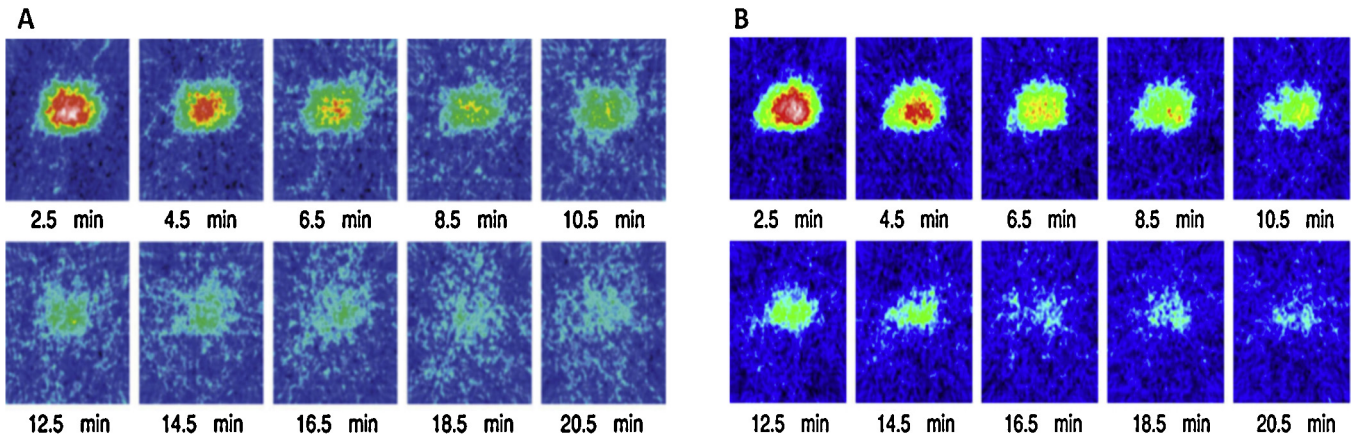

Fig. 3. (A) This figure shows the typical 2D electron spin resonance images (ESR) of the distribution of MC-PROXYL (3-methoxycarbonyl-2,2,5,5-tetramethyl-pyrrolidine-1-oxyl, a blood brain barrier-permeable nitroxyl spin probe) in the brain of spontaneously hypertensive rats (SHR). ESR was measured at 2.5, 4.5, 6.5, 8.5, 10.5, 12.5, 14.5, 16.5, 18.5 and 20.5 min after injection with MC-PROXYL (isolated 30 s after measurement). (B) A long-term supplementation with fermented papaya preparation resulted in a rapid decay of MC-PROXYL in FPP-supplemented SHR. All ESR images are reproduced in 16 colors with signals lower than 10% of the maximal signal intensity detected in all slices was regarded as noise.

From [34] with permission.

has been reported to modulate cell apoptosis through bax/bcl-2 sensitive pathways [30].

Given the complex interaction between chronic inflammation and oxidative stress mechanisms involved type 2 diabetes [31,32], therapeutic interventions involving antioxidants could theoretically reduce the risk of base mutations and vulnerability of cells to undergo cell transformation. The intriguing electron spin resonance data of Aruoma et al. [33] and Yoshino et al. [34] provides ample evidence that FPP is one such antioxidant (Fig. 3,4 and 5). The protective effect of FPP on oxidative damage in the brain was confirmed by measuring the decay rate constant of MC-PROXYL (3-methoxycarbonyl-2,2,5,5-tetramethyl-pyrrolidine-1-oxyl, a blood brain barrier-permeable nitroxyl spin probe) in isolated brain of spontaneously hypertensive rats, a well characterized animal model of oxidative stress. Given that major organs (brain, heart, kidneys) are protectively enrobed in a rich oxidizable polyunsaturated fatty acid sheath and constantly demand a permanent oxygen and glucose supply, they are easily prone to oxidative stress attack. The ability of FPP to protect such major organs challenged by iron, peroxyl radicals or by ischemia reperfusion injury to overcome lipid peroxidation are widely reported [35–37].

Nitrilotriacetic acid (NTA) is a common chemical component used in the treatment of drinking water and to a lesser extent in photography, paper and cellulose manufacturing, metal plating and in domestic detergents. NTA toxicity increases when it is chelated to metal ions such as the interaction with [Fe^{+3}] ions [38,39]. Ferric nitriloacetate chelate (Fe-NTA) has been reported to trigger hemochromatosis and insulin resistance via the oxidative damage of cellular lipids, proteins and DNA [39] thus it is an ideal model for assessing the anti-genotoxic effect of potential dietary antioxidants [40] prompting the work of Rimbach et al. [41]. FPP was demonstrated to effectively counteract Fe-NTA plus H_2O_2 induced genotoxicity in human T-cell leukocytes [41]. A similar protective effect was reported in a human cohort diagnosed with HCV-related cirrhosis [42] and chronic gastritis [43] supplemented with FPP for 6 months. This was evidenced by the reduction in circulating levels of 8-hydroxy-2′-deoxyguanosine (8-OHdG), a common marker of oxidative DNA damage. With the anti-genotoxicity activity of FPP being ascribed to its hydroxyl scavenging and iron chelating properties [41], FPP could dictate the extent of oxidative damage inflicted on DNA through the modulation of mitogen activated protein kinases (MAPKs) [44]. FPP was found to attenuate Akt and p38 activation, hence prevent premature apoptosis of pheochromocytoma (PC12) cells exposed to H_2O_2 [33] (Fig. 4). Several human interventional supplementation studies also confirm that FPP greatly influences transcriptional modification of key antioxidant enzymes and DNA repair genes (glutathione-s-transferase, superoxide dismutase, catalase, glutathione reductase, hoGG-1, heme oxygenase-1) [45,46]. Similarly, the toxicity of carbon tetrachloride (CCl_4) was found to be overcome by an aqueous extract of ripe mature papaya seeds [47,48]. That a marked reduction of ALT, AST, urea and creatinine levels were also reported (biomarkers of hepatocellular injury and renal function) provides additional evidence of the protective effects of *C. papaya* [47,48]. The studies referred to above provide the basis of the potential application of papaya-based preparations such as FPP that could be adopted in a clinical setting for the management of liver and kidney cancers given the potential involvement of oxidative stress.

Common combinational therapies in modern cancer management include radiation and chemotherapy, however oxidative injury as a result of ionizing radiation exposure can damage cells, especially those of the skin, spermatogia and hematopoietic stem cells [49–51]. Evidence from a randomized open clinical trial assessed the efficacy of an enzyme preparation containing chymotrypsin and papain derived from the latex of unripe papaya in reducing the acute side effects of radiation therapy in a cohort with advanced cancer of the uterine cervix. Oral supplementation of this preparation could significantly reduce the intensity of side effects associated with acute radiation therapy (e.g. skin reactions, gastrointestinal discomfort and site-specific mucosal reactions) [52]. Acute headaches, vomiting, nausea and occasional bouts of unconsciousness are also commonly experienced during chemotherapy. These unpleasant side effects were found to be overcome through a short term administration of FPP in children suffering from acute myeloleukemia [53], further sustaining the plethora of literature underlining the protective effect of papaya-based preparations. Thus FPP may benefit the unpleasant secondary effects associated with intense anti-cancer therapies.

The nature of the chemical modifications that *C. papaya* undergoes during biofermentation is not yet fully characterized. The amino acids which prevail in both fresh and fermented papaya in particular aspartic acid, glutamic acid, glycine and methionine (Table 1) could contribute to the synthesis of endogenous antioxidants notably glutathione and glutathione peroxidase (GPx) observed in literature [30,44–46,54–57]. The ability of FPP to permeate the small intestine and act in synergy with other locally

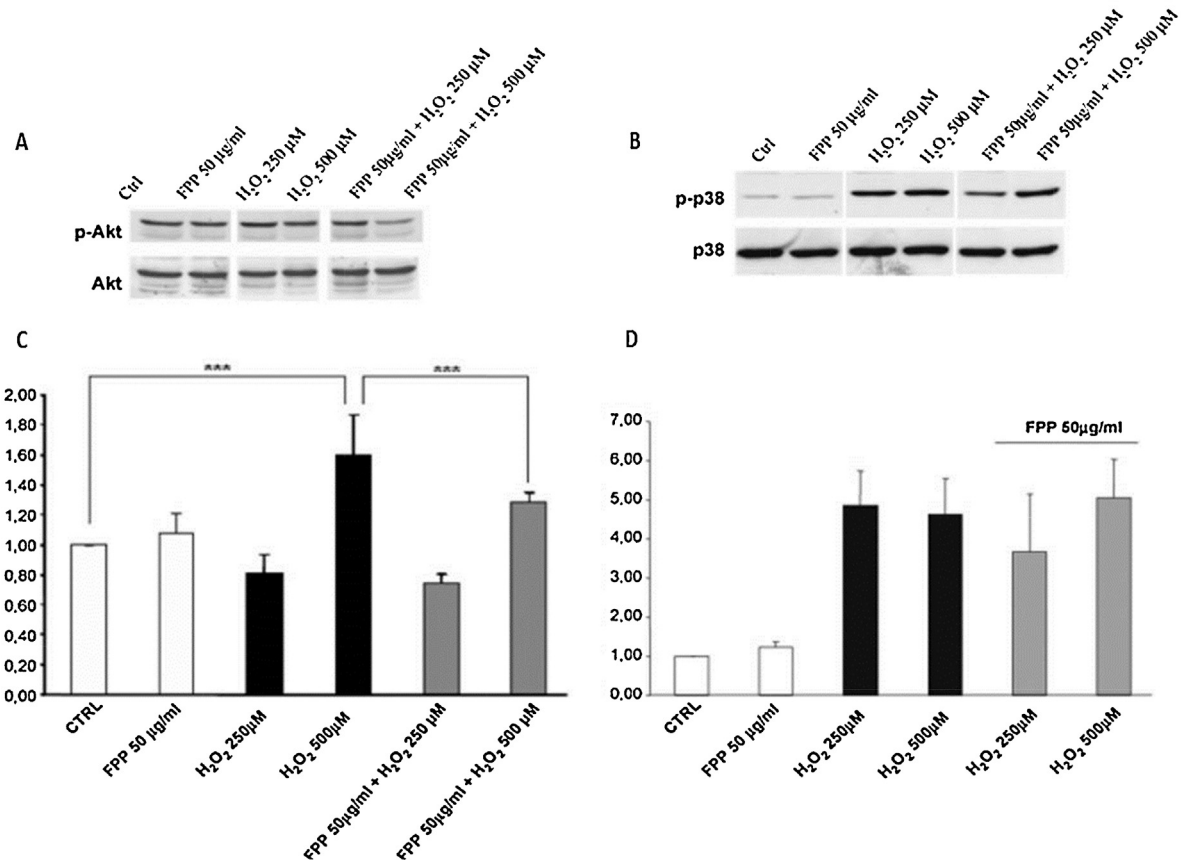

Fig. 4. (A) Western blot analysis of Akt phosphorylation. (B) Western blot analysis of p38 phosphorylation. (C) Graphical representation of the inhibitory effect of a 23 h pre-treatment with FPP (50 μg/ml) followed by a 1 h H_2O_2 (250 μM and 500 μM) induced on Akt phosphorylation. (D) Graphical representation of the inhibitory effect of a 23 h pre-treatment with FPP (50 μg/ml) followed by a 1hr H_2O_2 (250 μM and 500 μM) treatment on p38 phosphorylation. Data represents the O.D. normalized to control of $n = 4$ independent experiments. Values are expressed as mean ± S.E.M; ***indicates $P < 0.001$.
From [33] with permission.

present dietary antioxidants (such as vitamin E and C, α-tocophenol or β-carotene) could equally contribute to the overall boost in in vivo antioxidant status documented in literature [44,57]. The study, although of short term, clearly demonstrated that a component with antioxidant function could potentially be beneficial. Indeed longer and larger bioefficacy studies to establish clear links between the effects of FPP on the transcriptional modification of key enzyme gene expression would provide deeper

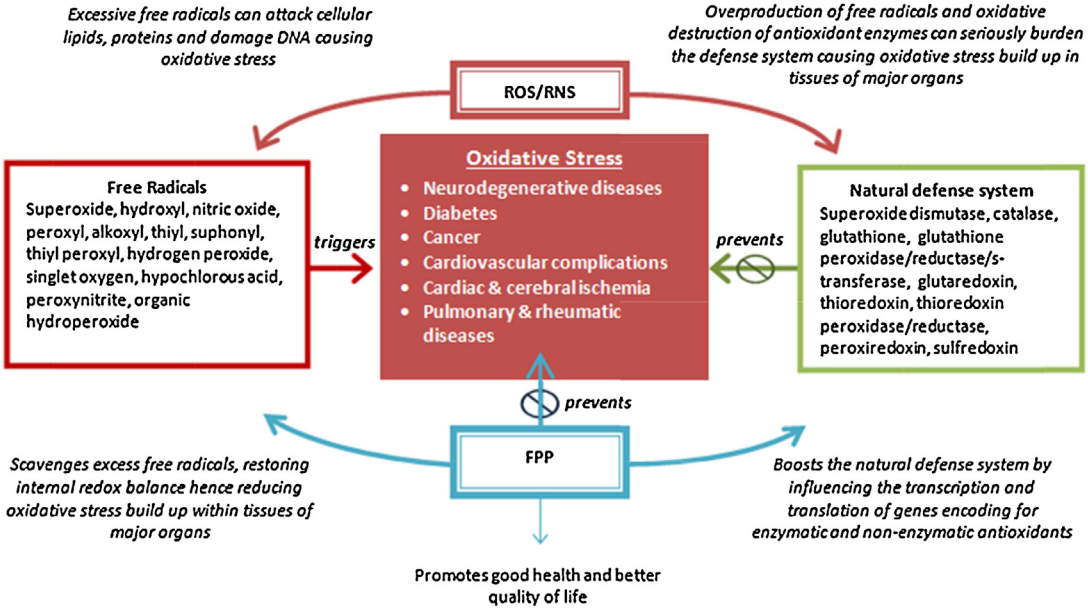

Fig. 5. A simplified outline of the beneficial properties of fermented papaya preparation (FPP).

Table 1
Composition of fermented papaya preparation. Analyzed by the Japan Food Research Laboratories, Nagoya, Japan.

General compounds	Quantity/100 g	Amino acids	Quantity (mg)/100 g
Carbohydrate	91.3 g	Arginine	16 mg
Protein	0.3 g	Lysine	6 mg
Fat	Non-detected	Histidine	6 mg
Dietary fiber	Non-detected	Phenylalanine	12 mg
Moisture	8.4 g	Tyrosine	8 mg
Energy	366 kcal	Leucine	18 mg
Vitamin B6	17 μg	Isoleucine	10 mg
Folic acid B9	2 μg	Methionine	5 mg
Niacin	240 μg	Valine	14 mg
Sodium	0.5 mg	Cysteine	Not detected
Iron	0.29 mg	Alanine	13 mg
Calcium	2.5 mg	Glutamic acid	37 mg
Potassium	16.9 mg	Serine	11 mg
Magnesium	4.6 mg	Theronine	8 mg
Copper	14 μg	Aspartic acid	23 mg
Zinc	75 μg	Tryptophan	2 mg
Glycine	11 mg	Proline	12 mg

Adapted from [34].

understanding of the nutrageonomic mechanisms involved [44]. This would position FPP's benefits in the domain of cancer chemoprevention and treatment.

3. Reducing the risk of cancer through the treatment of diabetes

Diabetes is a condition that eventually requires the need for exogenous insulin therapy. Emerging evidence from observational studies that evaluate the risk of developing cancer in diabetic patients who are being treated for their disorder versus those not receiving anti-diabetic medication has now established that prolonged intake of insulin analogs, sulfonylurea and pioglitazones (amongst others) indeed boosts the risk onset of various cancers [58,59]. Despite the benefits such drugs offer in treating diabetes, warnings issued by the Food and Drug Administration (FDA) and Health Canada have raised curiosity of their long term safety. Using data from a large UK general practice database Azoulay et al. [60] recently reported the exclusive use of pioglitazone was associated with an increased rate of bladder cancer by 83% (rate ratio: 1.83, 95% CI 1.10–3.05) in type 2 diabetics, a risk which was twice as higher than those prescribed rosiglitazone. Experimental cancer in a rodent model has implicated chronic bladder irritation as a likely result of pioglitazone-induced calciferous crystal formation rather than peroxisome proliferator activated receptor gamma (PPARγ) interaction in urothelial cells [61]. Similarly, a higher incidence of pancreatic and liver cancer was detected in patients prescribed sulfonylureas [62]. The gradual failure of secretary pancreatic beta cells in patients with long standing diabetes urgently calls for exogenous insulin therapies. However, novel revelations of the association between incidence of malignancy and insulin continue to emerge. Comparisons between insulin analogs (such as aspart, lispro and glargine) to human insulin showed that prolonged glargine treatment was found to have a higher dose-dependent risk. In a Netherlands study, 2.5 million out-patient pharmacy records were analyzed. Out of 19,337 insulin users, 878 were diagnosed having cancer, glargine was revealed to be associated with the number of breast and prostate cancer cases reported (hazard ratio: 1.58 and 2.76 respectively [63]). Luo et al. [64] reported lung cancer incidence (hazard ratio 1.71, 95% CI: 1.15–2.53) to be significantly higher in postmenopausal women especially those using insulin. Somewhat surprisingly, the outcome of metformin therapy in type 2 diabetes is documented to reverse the cancer related mortality, especially for those exposed to long term metformin treatment [65]. The dual properties of metformin are mediated via the activation of AMP-activated protein kinases (AMPK) [66]. Thus there is a need to better understand the etiological role of different anti-diabetes therapies in cancer and the possibility of adopting FPP as a novel phytonutraceutical that can impact insulin secretion or action without the risky exposure to certain cancers as posed by conventional drugs.

4. Folklore practices of using *C. papaya* in the management of diabetes

Although increasing number of plants are being studied scientifically with documentation of their anti-hyperglycemic, antioxidant and insulin stimulating activities [67,68], the emergence of scientific studies supporting the anti-diabetic properties of fresh *C. papaya*, especially for the unripe pulp and seed is of interest. The anti-hyperglycemic effect of papaya is thought to target pancreatic beta cells by boosting their sensitivity to insulin at the same time inhibiting α-amylase and α-glucosidase [69] a response which bears much resemblance to that of glibenclamide, a second generation sulfonylurea. The contribution of flavonoids, tannins and alkaloids present in various parts of papaya are also suspected to play an important role [70]. Indeed there exist many anti-hyperglycemic drugs that normalize plasma glucose levels, but there is a dearth of drugs that allow simultaneous correction of the lipid profile. Hence, since several studies have demonstrated that extracts of both fresh and fermented papaya could exhibit simultaneous hypoglycemic and hypolipidemic activities in both animal and humans models of type 2 diabetes, this makes papaya fruit an important yet unrecognized asset in dietary management of diabetes which deserves evaluation at molecular level [71–74]. The review by Fauziya and Krishnamurthy [75] looks at the papaya (*C. papaya*) as source material for anticancer and features a summary of the data on the cytotoxic effects of *C. papaya* extracts tested on several cell lines.

With the rising concern of the implication of anti-diabetes drugs in cancer threatening to burden the global health care system, the application of FPP for the dietary management of diabetes has become quite appealing to both the medical community and health-conscious consumers alike. The hypoglycemic effect of FPP was investigated by Danese et al. [73] in an open randomized clinical trial in which 3 g FPP/day for 2 months could significantly reduce fasting and post-meal glucose levels in both normal and type 2 diabetic patients. These findings were further supported by Collard and Roy [74] where FPP (0.2 g/kg/8 weeks) could indeed attenuate the gain in blood glucose of db/db mice. These findings do not directly prove the anti-diabetes activity of FPP, nonetheless they are consistent with the hypothesis that FPP may work in synergy with

oral hypoglycemic drugs as adjunct therapy. A supplementation study was carried out on a multi-ethnical pre-diabetic population in which biomarkers of oxidative stress were considered as clinical end-points [57].

Low grade inflammatory states experienced during diabetes have been reported where the excessive induction of inflammatory cytokines (TNF-α, interleukin (IL)-6, IL-1), chemokines (IL-6), and pro-inflammatory transcription factors (NF-kB) regulated by ROS and major mediators of cancer progression [18,31] (see Fig. 2). The metastatic potential of chemokines and chemokine receptors and the use of pro-inflammatory cytokines as predictors of several cancers have been reviewed [18]. The direct suppression of inflammatory molecules in attempt to reduce cancer progression has been demonstrated to be detrimental. That FPP could target ROS generation as a means of regulating inflammatory response pathways was the subject of several investigations. Several studies have successfully demonstrated FPP to be a valuable immune modulator. For example: the synergistic interaction of FPP with IFN-γ has been reported to regulate the secretion of tumor necrosis factor-α (TNF-α), one of the central regulatory cytokines in macrophage anti-microbial activity, and induce the production of nitric oxide (NO) [46,76,77]. Even though excessive NO may be detrimental to our body, it is also an indispensable vasodilator, neurotransmitter and an important agent against tumorigenic cells and pathogenic invasions. The process of wound healing is greatly slowed in diabetic individuals. Extensive epidemiological surveys have indicated that at least 70% of all lower limb extremity amputations were performed on type 2 diabetics, of which the majority could have been avoided through simple low-cost preventive measures [78,79]. A constant state of hyperglycemia coupled with a deficient immune system, narrowed blood vessels and low NO availability heightens the risk of developing gangrene, sepsis or ulcerations [80]. Papain isolated from the latex of unripe papaya pulp is documented to be one of the earliest substances used in wound care and chronic skin ulcer therapy for its anti-bacterial and fibrinolytic properties [81,82]. Collard and Roy [74] found that a supplementation of fermented papaya could in fact accelerate wound healing in db/db mice by elevating levels of nitric oxide, IL-6, TNF-α and circulating CD38 at the wound site. That FPP could positively influence inflammatory pathways provides a means of targeting diabetes and cancers that are governed by acute inflammation is the center of on-going investigation.

The following abstract comments from Arcidiacono et al. [9] remains seminal for the purpose of this perspective paper: “insulin resistance is common in individuals with obesity or type 2 diabetes, in which circulating insulin levels are frequently increased. The mechanisms for this association are unknown, but hyperinsulinaemia (a hallmark of insulin resistance) and the increase in bioavailable insulin-like growth factor I appear to have a role in tumor initiation and progression in insulin-resistant patients. Insulin and IGF-I inhibit the hepatic synthesis of sex-hormone binding globulin, whereas both hormones stimulate the ovarian synthesis of sex steroids, whose effects, in breast epithelium and endometrium, can promote cellular proliferation and inhibit apoptosis. Furthermore, an increased risk of cancer among insulin-resistant patients can be due to oxidative stress that can damage DNA contributing to mutagenesis and carcinogenesis”. There remains the possibility that the abundance of inflammatory cells in adipose tissue of obese and diabetic patients may promote systemic inflammation which can result in a pro-tumorigenic environment (see Fig. 2).

The report of Ranc et al. [83] on cancer mortality rates among patients with diabetes mellitus: effect of diabetes duration and treatment, brings eminence to the forgoing discussions. The study was aimed at exploring the differences in survival among cancer patients with diabetes prior to cancer diagnosis compared with cancer patients without diabetes as well as examining the association between different types of glucose lowering therapies and survival after cancer diagnosis, and how this potential association varies with the duration of diabetes and by time since diagnosis of cancer. Ranc et al. [83] concluded that the mortality risk of cancer patients with pre-existing diabetes experience was four times higher than those without diabetes. The higher mortality seen among cancer patients treated with oral hypoglycemic agents or insulin is in accordance with the existing evidence that more intensive diabetes treatment reflects a larger degree of comorbidity at the time of cancer diagnosis, and hence poorer survival [83]. Thus it is crucial that cancer patients with diabetes benefit from optimal diabetic treatment as well as cancer-specific therapy, whereupon a close collaboration between oncologists and endocrinologists is vital to optimize the therapeutic outcome and compliance.

5. Conclusion

Fermented papaya preparation has a beneficial prophylactic potential that can be clinically exploited as a nutraceutical for the dietary management of both diabetes and cancer. Even though conventional biochemical hypoglycemic agents such as insulin analogs, sulfonylurea and rosiglitazones (amongst others) are the mainstay of diabetes treatment regime and are effective in controlling hyperglycemia, they have many prominent side effects which includes the onset of cancer and failure to exert prolonged hypoglycemic effects. Fermented papaya preparation with its demonstrated efficacy in controlling blood glucose, excessive inflammation and modulating free radical-induced oxidative damage triggers of liver, bladder, breast and prostate cancers in type 2 diabetics, may mitigate the side effects of ensuing diabetes and cancer therapy.

Authors’ Contribution

Okezie I Aruoma, Jhoti Somanah, Emmanuel Bourdon, Philippe Rondeau and Theeshan Bahorun wrote/reviewed/edited the manuscript. Okezie I. Aruoma is actively involved in biomedical research involving fermented papaya preparation for the Osato Research Institute, Gifu, Japan.

Conflict of statements

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