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REVIEW ARTICLE

Is honey a plausible candidate for the prevention of in-stent restenosis?

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Summary

Coronary artery disease (CAD) is the major cause of death worldwide. Initially balloon angioplasty (BA) seemed to be a commonly available treatment for such disease. The major limitation of this method is restenosis. With the advancement of coronary stenting, the incidence rate of restenosis after ballon angioplasty has been greatly reduced. However, in-stent restenosis (accounting for 10- 40% of patients: mainly due to neointimal proliferation) has been a major drawback for such coronary interventions. To overcome this, drug eluting stents (DES) have evolved as a prospective proposal. Stents coated with various anti-inflammatory, anti-migratory or anti-proliferative agents are under investigation. These additives suppress the inflammatory response, smooth muscle cell migration and proliferation, thereby inhibiting in-stent restenosis. In this context, it is proposed that honey with diverse polyphenolic and flavonoid composition may prevent in-stent restenosis. Recent research demonstrated that crude honey could exert an anti-proliferative effect against various cancer cell lines such as colon, breast, bladder, oral squamous cell carcinoma and osteosarcoma. Flavonoids and phenolic compounds present in honey have been attributed individually for their anti-inflammatory and anti-proliferative potential and it has been shown that usage of honey in wound healing reduces inflammation and pain. Therefore, we hypothesize that crude honey which is rich in flavonoid and phenolic compounds may be a potential agent in preventing the in-stent restenosis. If our hypothesis is proven correct, honey will be a valuable candidate for saving millions of lives by preventing in-stent restenosis.

Keywords: Stent, re-stenosis, honey, coronary artery disease, drug eluting stents (DES)

Introduction

Coronary artery disease (CAD) is the major cause of death worldwide. According to a recent report from the American Heart Association, an estimated 785,000 Americans had a new coronary attack and about 470,000 had a recurrent attack during 2010. Further, for every 25 seconds an American will have a coronary event, which will result in death every minute (Roger, *et al.,* 2011). Balloon angioplasty has evolved as a promising mode of treatment for CAD. The major limitation of this method is restenosis. Restenosis mainly occurs due to acute elastic recoil, negative modeling and neointimal proliferation. With the help of the stenting procedure, acute elastic recoil and negative remodeling have been overcome, however neointimal proliferation remained unconquered (Hoffmann, *et al.,* 1996; Lowe, *et al.,* 2002).

To overcome this, drug eluting stents (DES) has evolved as a prospective proposal to prevent in-stent restenosis due to neointimal proliferation. In-stent restenosis is due to an inflammatory response because of trauma by stretching of the vessel wall. At the beginning of in-stent restenosis, platelets get activated by adhering to the stent struts, thereby inviting inflammatory cells to the site. This releases various cytokines and growth factors which in turn lead to smooth muscle cell migration and proliferation. Since in-stent restenosis is attributed to the inflammation and smooth muscle cell proliferation, stents were coated with various anti-inflammatory, anti-migratory or anti-proliferative agents (Versaci, *et al.,* 2004; Gaspardone, *et al.,* 2005; Li, *et al.*,2007). These drugs aim to suppress the inflammatory response, smooth muscle cell migration and proliferation, thereby inhibiting in-stent restenosis.

Although several agents were investigated only a few have evolved as promising agents for the control of in-stent restenosis. Among them, sirolimus and pacilitaxel seemed to be effective in preventing in-stent restenosis. However, there was no significant increase in target lesion revascularization rates detected at 1 and 2 year follow-up examinations (Virmani, *et al.*, 2003). Hence the search for promising new drugs with better properties to prevent in-stent restenosis continues.

Honey is one of the most commonly available foodstuffs since ancient times. Honey is rich in levulose and dextrose which justifies its major use as "sweeteners". Besides sugars, honey also contains various constituents like vitamin C, enzymes, minerals, proteins, flavonoids, phenolic compounds and other phytochemicals depending upon the origin of the honey (Jaganathan, *et al.*, 2009a, and 2009b). Honey not only finds a role in domestic needs but also in medicinal applications. Research findings indicate the anti-microbial activity of different honey types. Moreover honey has been used for treating peptic ulcers, gastroenteritis, methicillin-resistant *S. aureus* (MRSA) and tinea infections (Haffejee, *et al.*, 1985; Rademaker, *et al.*, 1993; Al Somai, *et al.*, 1994). Honey has been noted for its wound healing properties for a long time. It has been used as a topical agent for skin burns, ulcers and wounds. It has been shown that usage of honey in wounds reduces inflammation and pain (Bulman, 1955; Hutton, 1966; Cavanagh, *et al.*, 1970; Blomfield, 1973).

Recent research concluded crude honey could exert antiproliferative effect against various cancer cell lines like colon, breast, bladder, oral squamous cell carcinoma and osteosarcoma (Tarek, *et al.*, 2003; Jaganathan, *et al.*, 2009; Jaganathan, *et al.*, 2010; Ghashm, *et al.,* 2010). Flavonoids and phenolic compounds present in the honey have been attributed individually for their anti-proliferative potential (Jaganathan, *et al.*, 2009b). It has been shown that usage of honey in wound healing reduces inflammation and pain (Bulman, 1955; Hutton, *et al.*, 1966; Cavanagh, D *et al.*, 1970; Blomfield, 1973).

Hypothesis

The fact that honey possesses anti-oxidant, anti-inflammatory and anti-proliferative properties makes it an exciting agent in the biomedicine field. We hypothesize that crude honey has been bestowed with the necessary attributes to prevent in-stent restenosis. If our hypothesis is proven correct, honey will be a valuable candidate for saving millions of lives by preventing in-stent restenosis.

Validation

The feasibility of our hypothesis could be evaluated experimentally. Initially on the preclinical level, honey may be tested for its antiproliferative activity against smooth muscle cells. To evaluate the biocompatibility and efficacy, honey coated stents may be placed in an animal model to estimate its efficiency in the reduction of neointimal hyperplasia and also to determine whether honey elicited any proinflammatory responses. Further experimentation could be extended to test the hypothesis clinically. A study may be designed with two study groups containing 24 patients each. The selection criteria for both groups would include patients with a long lesion, small vessel and restenosis. Patients in group I would receive a stent eluted with honey, whereas those in group II would receive a sirolimus-coated stent. Techniques such as intravascular ultrasound and angiography must be used to assess the neointimal hyperplasia after implantation of drug-eluting stents. Moreover, clinical endpoints like major adverse clinical event (MACE), target lesion revascularisation rate, myocardial infarction and death rate must be recorded and the comparisons between the two groups made.

Discussion

To draw theoretical support for the hypothesis, literature discussing the antiproliferative, anti-inflammatory, prohealing nature and antithrombotic of honey and its constituents is discussed. Recent research on the antiproliferative effect of crude honey against various cancer cell lines has been published. Honey inhibited the proliferation of HCT 15 and HT 29 colon cancer cells by arresting cells at sub-G1 phase by depleting the intracellular thiols and increasing the ROS generation (Jaganathan, *et al.*, 2009c). Similarly honey was found to be capable of arresting the proliferation of breast cancer cells (MCF-7) (Jaganathan, *et al.*, 2010a). Honey has also proven effective in suppressing the growth of bladder cancer cells, oral squamous cell carcinoma and osteosarcoma (Tarek, *et al.*, 2003; Ghashm, *et al.,* 2010). Furthermore, honey was found to be effective when administered intralesionally or orally in the MBT-2 bladder cancer implantation models. There was also a significant difference between the final tumor volume ($P < 0.05$) in the intra lesion (IL) honey-treated groups (IL 6% honey) compared to the IL saline group (Tarek, *et al.*, 2003). Jaganathan *et al.,* 2010b showed when honey containing higher phenolic content was administered intraperitoneally (i/p at 25% (volume/volume), the maximum tumour growth inhibition was found to be 39.98% in the Ehrlich ascites animal model. Research conducted by Gribel and Pashinskii (1990), indicated that honey exhibited moderate antitumour and significant antimetastatic effects in five different strains of rat and mouse tumours. Moreover, the antitumour activity of certain chemotherapeutic drugs such as 5-fluorouracil and cyclophosphamide was also facilitated by the honey. These experiments provide a rudimentary evidence for the antiproliferative nature of the honey.

Honey contains some minor constituents like flavonoids and phenolic compounds, which are efficient in inhibiting cancer cells. Caffeic acid, caffeic acid phenyl esters, chrysin, galangin, quercetin, kaempferol, acacetin, pinocembrin, pinobanksin and apigenin (which

are present in honey) have demonstrated antiproliferative effect against different cancer cell lines (Jaganathan, *et al*., 2009a). Besides, phenolic constituents of honey like quercetin, caffeic acid phenethyl ester (CAPE), acacetin, kaempferol, galangin have demonstrated remarkable potential in the treatment of cardiovascular diseases. Many epidemiological studies have shown that regular intake of phenolic compounds is associated with reduced risk of heart diseases (Khalil, *et al*., 2010a & b). Moreover quercetin, one of the flavonoids found in the honey, has shown cardio-protective effects. It was found to inhibit the angiotensin-II mediated JNK activation and Akt-phosphorylation which are attributable for rat aortic smooth muscle cells hypertrophy (Yoshizumi, *et al*., 2001).

Sirolimus and pacilitaxel are not only found to inhibit the smooth muscle cell proliferation and migration but also impede the normal healing process by retarding reendothelialization. To override this obstacle, drugs with prohealing potential may be a solace for percutaneous coronary intervention (PCI). Honey has been recognized for its wound healing properties since ancient times. It has been used as a topical agent for skin burns, ulcers and wounds. Repeated use of honey deodorizes the wound and also promotes healing without further tissue damage, while withdrawing the previous wound dressing (Burlando, *et al*., 1978; Armon, 1980; Bose, 1982; Dumronglert, *et al*., 1983; Kandil *et al.,* 1987). It has also been reported that, when given orally, honey lowers plasma prostaglandin concentrations in normal individuals (Al Waili, *et al*., 2003). Honey has been endowed with the ability to modulate the production and quenching of free radicals which had been attributed in resolving the state of inflammation typifying chronic wounds thereby promotes healing (Jackson, *et al*., 2006). Activation of peroxisome proliferated activated receptors (PPARs) family (PPAR α, β/δ, and γ) by their ligands have been shown to contribute wound healing (Tan, *et al.,* 2005). Recent observations suggested the agnostic activity of manuka honey against PPARγ which partially supports our hypothesis (Hicks, *et al*., 2008).

Coronary stenting invites platelet aggregation which leads to stent thrombosis. Both animal and human trials of stent implantation lead to increased platelet aggregation (Inoue, *et al.,* 2006). *In vitro* studies using honey (sunflower honey from USA, clover honey from Australia and Salvation Jane [*Echium vulgare*] honey from Australia) showed strong inhibition of platelet aggregation caused by ADP [adenosine diphosphate]. Further they postulated that honey may be used for prophylaxis in patients with cardiac or cerebral infarction (Shimizu, *et al.,* 1990).

Hence crude honey may have the potential to inhibit in-stent restenosis. If our hypothesis is proven correct, honey will be a valuable candidate for saving millions of life by preventing in-stent restenosis. Nevertheless an important note to consider while using honey is its quality. The quality of honey is controlled by various factors like its origin, production and preservation (Jaganathan, *et al.,* 2009d).

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