

Bees and Honey against Tuberculosis?

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Drug resistant tuberculosis is increasing. Its treatment is costly and lengthy. New rapid methods of detecting drug resistance (e.g. PCR), are helpful but too costly to be used in developing countries. Several tools with improved sensitivity and speed of diagnosis have been endorsed by the World Health Organization (WHO) [1,2], as they allow early epidemiological and therapeutic interventions. However the current process of endorsement is necessary but insufficient [3]. The International Standards for tuberculosis Care discourage the use of serological tests in routine practice and no international guidelines recommend their use [4]. Development of new drugs is also very costly and not seen as a priority in the market orientated economics of the pharmaceutical industry [5]. The emergence of multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB) and extensively drug-resistant *Mycobacterium tuberculosis* (XDR-TB) strains has made many of the currently available anti-tuberculosis drugs ineffective. Tuberculosis caused by *Mycobacterium tuberculosis* complex remains one of the major public health problems, especially in developing countries. Recent resurgence of pulmonary tuberculosis in developed countries like United States posed a threat to the medical community due to resistant strains. Consequently WHO looked to traditional medicine [6]. Tuberculosis is nowadays the most lethal infection in the World. Several signature compounds for *Mycobacterium tuberculosis* and *Mycobacterium bovis* have been identified [7] which may offer a solution, if the compounds can be shown to reliably characterize infection through sampling of human breath [8]. Electronic odorant detection systems so far appear inadequate for the task of TB detection [9,10]. A recent study by researchers at Christchurch's New Zealand Institute for Plant and Food Research Limited shows that the bees can detect even traces of sweet-smelling volatiles produced by *Mycobacterium tuberculosis*. They concluded that potential exists for trained honeybees in non-invasive diagnostic tests for TB [11]. Avicenna almost 1000 years ago recommended honey as one of best remedies in the treatment of tuberculosis [12]. According to Sharma et al. [13], honey with anti-tubercular treatment minimizes the adverse drug reactions induced by Anti-TB drugs in newly diagnosed sputum acid fast bacilli positive pulmonary positive tuberculosis patients. It has been demonstrated that the growth of mycobacteria from positive cultures and from positive smears of affected patients was inhibited by honey [14]. But the mechanism by which honey act is unclear. Much smaller changes in oxygen tension affect the antibiotic killing of bacterial persisters (e.g. *M. tuberculosis*). Although these small reductions in oxygen tension do not alter the kill kinetic of the larger antibiotic-susceptible population, these changes dramatically affect the size and survival ability of the smaller persister subpopulation. This subpopulation remains vulnerable to the common antibiotic-induced hydroxyl-radical-mediated death pathway if sufficiently high free-radical concentrations can be maintained [15]. Generation of hydroxyl radical is a common property of honeys of European, North and South American origin [16,17]. The hydroxyl radical-based mechanism of honey action did not discriminate between antibiotic-sensitive and antibiotic-resistant bacteria [17]. Hydrogen peroxide (H₂O₂), one of the Reactive oxygen intermediates generated by macrophages via the oxidative burst, was the first identified effector molecule that mediated mycobactericidal effects of mononuclear phagocytes [18]. It is well

known that honey when diluted is a glucose/glucose oxidase generating H₂O₂ system [19,20]. TLRs (Toll like Receptor) are involved in cellular recognition of mycobacteria, expression of TLR2 or TLR4 conferred responsiveness to both virulent and attenuated *M. tuberculosis* [21]. Honey has been found to stimulate monocytes *in vitro* to release TNF- α [22]. This was determined to be due to a 5.8 kD component in honey which acts via the TLR-4 receptor [23]. Mycobacterial infection and pro-inflammatory cytokines increase surface expression of TLR-2 [24]. Interestingly it has been shown that Honey stimulates inflammatory cytokine production [25,26]. The above cited mechanisms may act synergistically they may also be implicated in the same process with different reaction time courses.

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