Adverse effects of antioxidants

The letter on 'adverse effects of antioxidants'[1] referring to an earlier report[2] was interesting. However, the nature of adverse effects expected from consuming antioxidants (rich preparations), β-carotene or vitamin-E as antioxidants was not clearly illustrated. Rather, their therapeutic application based on antioxidant properties is being increasingly advocated for beneficial effects in various disease conditions. The importance of antioxidants, their mechanisms of action and the paradox related to β-carotene and vitamin-E are available in the literature[3]. Furthermore, vitamin-E, etc. have provided important insights into the design and development of novel therapeutics based on antioxidant mechanisms. Several views[4,5] advocating the development of antioxidant-based drugs have provided various positive points in rationalizing their development for the treatment of diseases of multifactorial origin.

These advances have led to the development of several drugs based primarily on antioxidant mechanism for the treatment of various diseases[6,7]. These developments have also paved ways in understanding therapeutic properties/mechanisms of several traditional medicinal plants/preparations based on antioxidant properties for multiple therapeutic effects[8,9] and opened new avenues for their mechanism-based therapeutic applications. These traditional Eastern medicines have been used for thousands of years. Western medicine, however, has not yet used them therapeutically, even though their safety record is exceptional[10].

As far as the long-term data on the adverse effects of antioxidant therapy is concerned, there is also no medicine without side effects. The therapeutic application of a drug is decided on the basis of its therapeutic risk-and-benefit ratio. The more it skews towards the latter side, the broader and better is the drug/composition's therapeutic range and safety. This holds true for the antioxidant-based drugs also, as they are being reported to possess broad spectrum multiple therapeutic properties[7–10]. The concerns therefore, of adverse effects of antioxidants[1] do not appear sound. Moreover, the development of a drug relates to the benefits of suffering humankind. The search and development of effective and multiple-mechanism based therapeutics from traditional medicinal practices are the requirements of the day. Nayeemunnisa and Kumuda Rani[2] have made positive efforts in delineating the beneficial therapeutic effects of traditional medicine, *Cichorium intybus*. Such efforts should be encouraged rather than propagating the adverse effects without substantial reasons.

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Conceived conclusions in favour of GM cotton? – A riposte to a paper in *Science*

Conflicting scientific, public and farmer opinion on the benefits of GM crops is well known and widely documented. The science behind GM crops is not under dispute, but their adaptation to the target site, consequent changes in the bio-environment, promised benefits and their sustainability certainly are.

A recent article that appeared in *Science* by Qaim and Zilberman (Q&Z)[1] has resuscitated the controversy by drawing questionable results and incongruous inferences from an analysis of yield trial data. 395 trials were laid during 2001 on farmers' field across seven Indian states. (names not given) by the Mahyco–Monsanto group to test their *Bt*-cotton hybrid. A non-*Bt* counterpart and a popular check (details not given) were also raised in contiguous plots of 646 m^2 each. Evaluating a sample of 157 trials from three states, Q&Z observed a reduction in pesticide use by 70% in *Bt* cotton and yield increase by 80 and 87% over non-*Bt* cotton and popular check. Interpreting that 'a general germplasm effect (not defined) was more or less negligible' and 'the yield gains are largely due to the *Bt* gene itself', Q&Z concluded that 'it will be important' for India 'to release additional *Bt* cotton hybrids so that the technology yield gains for farmers are not curbed by a general germplasm disadvantage'.

Unconvinced by the conclusions, scanty details and a number of bugs in the table presenting yield and insecticide data in the paper, we contacted the senior author who kindly answered all our queries. We present below our critical review in the new light of the author's response (mostly in italics).

The data are not only from actual field trials but also from those of a survey by the authors since *they did not entirely*

rely on Mahyco trial record, and needed additional information on input–output relationships and farm and farmer characteristics. Out of the seven states, Maharashtra, Madhya Pradesh, Tamil Nadu, Andhra Pradesh, Karnataka, Gujarat and Rajasthan, the former three were selected. Resource constraint led to a random choice of 157 trial participants (out of 395) who were from more than 25 different districts. The sampled states occupied 45% of the total area under cotton[2]. This led Q&Z to believe that *the sample should be pretty representative for cotton growing in central and southern India.*

The Indian Council of Agricultural Research has classified the seven states into three zones for varietal evaluation based on varied edaphic and climate conditions. Unless specific premises exist for wide adaptation, varietal performance will be evaluated only in specific zones. Andhra Pradesh, as a state with large area under cotton and widely affected by its failure, must have been included on its own right in the study. The exclusion of Andhra Pradesh and Gujarat has skewed the findings towards Maharashtra, incidentally housing the seed source of *Bt*-cotton hybrid. Further the sample, instead of being just random, must have been to a design to ensure that it was representative. Just the area covered with no break-up even of the 157 trials across the sampled states, cannot justify its credibility. It is strange that many important details, gathered by us, were missing in their paper. Moreover, in a study seeking to test the benefits and efficiency of a new hybrid in farmers' fields, every one of the 395 trials ought to have been included and an analysis of variance followed by valid statistical test of significance of differences in yield done. Precluding a particular trial, could, for example, preclude the poor yield of the test hybrid in a farmers' plot. There is no room for a free mix-up of survey and field data. Logistics and funding restrictions are quite common but they cannot override scientific requirements. The restricted and skewed sampling would not leave any scope for applying the results of the study even to cotton growing southern and central states of India, let alone whole of India and the developing countries.

Gross plot size was used to extrapolate yield per ha from the data on *kapas collected by farmers themselves from variable pickings and kept with them.* Instead, yield must have been estimated on net plot sizes that should have been kept constant. The study by masking variable net plot and adjusting yield for uniform gross plot size has vitiated the conclusions.

Variation between the treatments (though stated to be minimal within farmers) and *between farmers' practices was very much present.* Q&Z say that *although the Bt cotton trials were carried out within a designed set-up, they were not controlled experiments. Farmers conducted the trials in their own way uninfluenced by the monitoring by agronomists.* But, regardless of *farmers harvesting several times on each plot, according to their own timing*, Q&Z observe econometric estimates reflected net yield effects. It is unreasonable to convolute the objective of testing the performance by farmers in their fields to bypass the basic minimum of required standards for test trials. Lack of norm for trials conducted by farmers, poor choice of non-*Bt* checks, multiple harvest of each plot suiting farmers' own timing, non-accounting for the variable number and the physiological stage of pickings, using uniform gross plot sizes for per hectare yield estimation ignoring variation in net plot sizes, obtaining yield data from *kapas* kept by farmers in their own way with possible deficiencies and, above all, econometric estimation of net yield effects are a few calamitous infirmities of the paper.

In an analysis of actual trial data, there is no scope for yield estimation, econometric or otherwise. No logic exists for expecting a regular distribution of farmers' yields, that too under a variety of acknowledged variation present in the study. Yet the figures in the paper show a smoothed distribution of yield–density functions and the relationship between insecticide use and crop losses. Though the density functions are not given, the very concept stands on infirm ground.

In terms of inputs other than pesticides, the paper states *there were no significant differences between the three treatments.* But the coefficient of variation (cv) for *Bt* hybrid, non-*Bt* counterpart and non-*Bt* check in the table of the paper is very high at 57.1%, 68.7% and 71.2%, respectively. Scientifically, no field experiment showing such high cv for yield will be considered fit enough for any worthy conclusion. But Q&Z say that such an observation *would be valid only for controlled experiments* (if the experiments are not controlled for valid comparison, what validity inferences can have is a moot question!). They explain that *solid differences that existed across different farmers made the standard deviations within each treatment pretty high, such a high cv would be very typical for farm survey data, and not surprising at all. The econometric estimates of production functions used in the paper helped to control them!* The authors continued that, *what was important then, was to carry out rigorous statistical tests for differences. When done, regardless of assumptions about (**un-**) equality of the variance, the differences were statistically significant, not only at 5% but also at 1% significance. Thus the conclusions are totally valid.* The mix-up of survey data with field trial data and blatant overruling of fundamentals of statistics and inference stand testimony for the low scientific base of the paper.

In the table of the paper, there are instances where the yields of popular check hybrids were inferior to the non-*Bt* counterparts. We argued that this anomaly would not have occurred if a proper choice of check hybrids were made in every location. In reply they say that, while *the names of all hybrids for the individual locations were available, they were not quite sure who exactly selected the popular checks. They were definitely not the best new hybrids for a particular location, but hybrids that local farmers were already familiar with. Most of these check hybrids are not from the Mahyco breeding program.* Without even confirming whether controls in the farmers' trials were appropriately chosen, the paper has made inferences on the test hybrid nullifying any scientific validity.

Regardless Q&Z insist that the *Bt* gene is of great value under the local conditions and should be incorporated in many different hybrids and varieties so that farmers under all agro-ecological conditions can benefit. This message at best is speculative.

We finally highlight the authors' advisory suggestion that the Indian regulatory authority should approve additional *Bt*-cotton hybrids well adapted to the agro-climatic conditions since the general germplasm effect of cotton on its yield is negligible in the absence of *Bt*-gene. If the single *Bt*-hybrid has such all-pervasive yield superiority across Indian subcontinent (first and then all develop-

ing countries), it should preclude the need for more hybrids as long as *Bt*-gene is the same in all hybrids! The response of the authors was a diabolical turn around. They say they *did not extrapolate numerical findings across India or other regions of the world and did not argue that the existing Bt hybrids are suitable for all parts of India*. *Bt*-hybrids showed also problems of coping with drought and viruses in a commercial scale but not related with the *Bt* gene. *The Bt gene (and other effective pest-resistance mechanisms) can lead to important yield effects in regions where pest pressure is high and is not well controlled by chemical pesticides. This hypothesis is backed by crop protection theory and empirical evidence from other countries. This is a very logical and simple statement, but it has not previously been articulated very clearly. Generally speaking, these conditions are often found in poor countries of the tropics and sub-tropics, especially in the small farm sector. Again, exact numbers should not be extrapolated*. It is then evident that they exhorted what they wanted regardless of the non-supportive data they analysed in support. It is perplexing that such a study could find its way to a journal like *Science* and it has come in handy to outscore a different reality of *Bt* cotton[3].

A study in Andhra Pradesh details the failure of *Bt* cotton hybrid, *Bt* Mech 162 (whether the same hybrid was used in the study of Q&Z is not known) both in small and large farms. A grievous farmer observed that *Bt* cotton fetched Rs 1300 a quintal compared to Rs 2600 of the popular variety Bunny. As the lint was less, seeds were more and the staple length was a clear 10 mm less than Bunny, there were not many buyers for *Bt* cotton. Despite being a newspaper report, it cites cotton scientists who concurred with the unfavourable market traits of *Bt* cotton. Similar results were also recently reported[3].

Reliable and consistent data in favour of GM cotton have yet to emerge from fair and large scale farmers' trial executed with every scientific norm. Equally important is the need to analyse all relevant data including quality parameters and market and marketability characteristics. Until then, GM crops and GM cotton can only enjoy a preferential lobby with little translation to ground reality.

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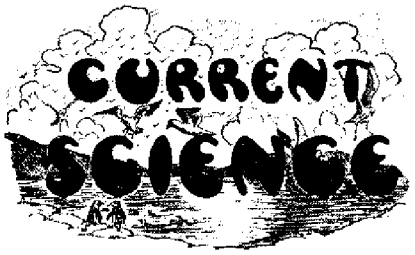

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Thiazole derivatives of sulphanilamide in monkey malaria

Certain sulphonamides like sulphanilamide, sulphapyridine and sulphathiazole have been shown to possess a curative property against experimental malarial infections in monkeys (See Dikshit, B. B. and Ganapathi, K., *J. Mal. Inst. Ind.*, 1940, **3**, 525). The author has tried two new thiazole derivatives of sulphanilamide (i) 2-N^1-sulphanilamido-5-ethylthiazole and (ii) N^1-methyl-sulphathiazole in several infections, bacterial and protozoal, including malarial infection in monkeys. The present note is concerned only about the malarial infection. The drugs were prepared by Ganapathi, K., Shirsat, M. V. and Deliwala, C. V., *Proc. Ind. Acad. Sci.*, 1941, **14A**, 630 in the Chemotherapy Department of the Haffkine Institute and supplied by that department.

Rhesus monkeys infected with *Plasmodium knowlesi* were used for the purpose. When the infection had reached a moderate degree (about 10 parasites per 10,000 R.B.Cs) the drugs were administered orally by a stomach tube. The dose administered was 1 g twice a day for 3 consecutive days. It was found that after administration of these drugs the parasites disappeared completely from the peripheral blood in 4 days. It was further observed that there was no relapse in the monkeys treated with these drugs while controls similarly treated with atebrine showed a relapse. The question of a radical cure was therefore investigated in the case of animals treated with 2-N^1-sulphanilamido-5-ethylthiazole. It was found that the blood of animals treated with this drug was not infective to normal animals 20 days after the disappearance of the parasites from the peripheral blood and the animals so treated were as susceptible to fresh infection as normal animals. It was therefore concluded that 2-N^1-sulphanilamido-5-ethylthiazole produces a radical cure in Rhesus monkeys infected with *P. knowlesi*. Cure of *knowlesi* infection in monkeys does not necessarily mean that the drug will be effective in human malaria also and investigations on this point along with the pharmacological investigations are being undertaken.

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