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# Sulforaphane from Broccoli Reduces Symptoms of Autism: A Follow-up Case Series from a Randomized Double-blind Study

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## Abstract

**Introduction:** Autism spectrum disorder (ASD) affects 1 in 68 children, is characterized by impaired social interaction and communication as well as restricted or repetitive behaviors, and varies widely with respect to its causes and presentations. There are no validated pharmacologic treatments for the core symptoms of ASD. The social, medical, and economic burdens of ASD on families and caregivers are profound. We recently showed in a small clinical trial that sulforaphane (SF) from broccoli sprouts could significantly reduce the behavioral symptoms of ASD.

**Methods:** After we completed the intervention phase of the original trial (2011–2013), many caregivers used over-the-counter dietary SF supplements in order to attempt to maintain improvements similar to those noted during the intervention. We periodically followed the progress of study participants through the summer of 2016.

**Results:** Families of 16 of the 26 subjects who received SF as part of the original study responded to requests for further information. Of these subjects, 6 did not continue taking SF supplements after the study. Nine of the 16 subjects are still taking an SF supplement and a 10th planned to. We present the edited testimonials of their caregivers in this case series.

**Conclusions:** Many parents and caregivers articulated the positive effects of SF, both during the intervention phase and in the ensuing 3 years reported herein. These observations may contribute to understanding ASD and to treatments that may alleviate some of its symptoms. Diet- and supplement-based therapies deserve careful consideration for their potential to provide vital clinical as well as biochemical information about ASD.

## Keywords

glucoraphanin, isothiocyanate, glucosinolate, prevention

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## Introduction

"Knock-knock… who's there? Knock-knock… who's there? Knock-knock… who's there? It was like he was stuck." Before he was 27 months old, "R" was a typically developing child and was easily able to finish telling his favorite knock-knock joke; but after an illness, his social and behavioral development halted, and he was soon diagnosed with autism (Autism Spectrum Disorder [ASD]). ASD is now estimated to affect 1 in 68 children

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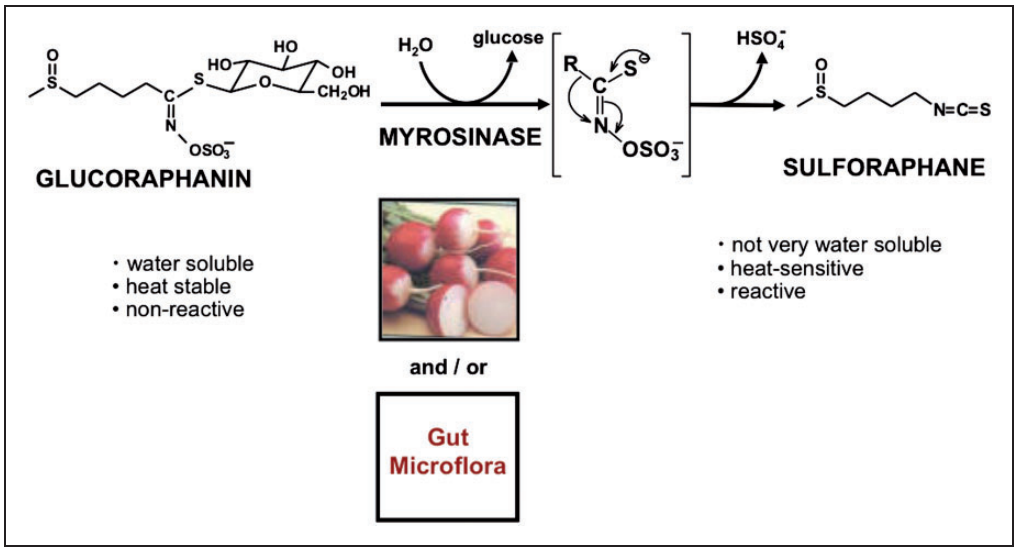


**Figure 1.** Conversion of glucoraphanin to sulforaphane. The enzyme myrosinase rapidly converts glucosinolates to their cognate isothiocyanates upon mastication of the plant tissue by humans. Myrosinase is found in cruciferous vegetables (eg, broccoli, wasabi, mustard, or radish) and also in human gastrointestinal flora. It is this latter source which is of most critical importance when human beings eat cooked broccoli or other cruciferous vegetables since cooking/heating inactivates myrosinase. The effects of sulforaphane on a variety of biochemical and molecular biomarkers and their clinical and preclinical applications have been recently reviewed[6,7].

in the United States by age 8 years,[1] and it exacts major emotional, financial, and social costs on the families of these children throughout their development, which continue into adulthood.

There is no cure for ASD, and despite advances in clinical therapies, there are no validated pharmacologic treatments for the core symptoms of ASD. Physicians often prescribe atypical antipsychotics to treat irritability and aggression in persons with autism. Aripiprazole (Abilify®) and risperidone (Risperdal®) are the only 2 medications currently approved in the United States by the U.S. Food and Drug Administration (FDA) to treat ASD. However, side effects of these drugs include extrapyramidal symptoms and can pose considerable risks such as dyskinesias (disorders in which involuntary tics and tremors occur), gynecomastia, and fatigue; increased appetite resulting in weight gain and obesity; and increased risk for diabetes. Further, due to CYP2D6 polymorphisms and variations in drug metabolism, predicting the frequency and magnitude of these side effects is difficult.[2,3]

Sulforaphane (SF; 4-methylsulfinylbutyl isothiocyanate) was isolated by Drs Paul Talalay and Yuesheng Zhang in 1992 at the Johns Hopkins University School of Medicine[4] and has since been studied extensively for its ability to prevent or delay the onset of various forms of cancer. SF is the chemoprotective, anti-inflammatory phytochemical that is prepared from broccoli sprouts[5] and has been successfully administered in a number of small clinical studies as diverse as cancer prevention, asthma, pulmonary function, alcohol toxicity, cognitive function, gastric colonization with *Helicobacter*, and ASD. SF-rich dietary supplements started to come on the market soon after our 1997 publication,[5] and they have proliferated in number and form ever since. There are now supplements rich in SF, many that are rich in *glucoraphanin* (GR; the biogenic precursor of SF), or in GR with *myrosinase* (MYR; the enzyme responsible for converting precursor to active moiety) (Figure 1). Some of these supplements were used by subjects following the intervention phase in our clinical trial of SF in ASD (see below) and in relating their observations, we have herein substituted trade names with the phrase "BSE," an acronym for *broccoli sprout [or seed] extract*.

A potential mechanistic connection between ASD symptoms and SF was identified based upon the widespread observations by families that improvement in ASD symptoms can be associated with a febrile illness in about 35% of patients.[8] This had been clinically validated by Curran et al.[9] Since SF had been previously shown to trigger a cellular heat shock response,[10–13] similar to the effects of fever, we felt that there might be an effect of SF on ASD symptoms. Thus, between 2011 and 2013, we conducted a small clinical study (NCT01474993) designed to assess whether SF would reduce or ameliorate the behavioral symptoms that are typical of individuals with ASD.[8,14,15] The published study evaluated behavior in 44 young men with ASD between the ages of 13 and 27 years. In this

double-blind randomized, placebo-controlled study, 26 participants randomized to SF received a weight-adjusted daily dose for 18 weeks, and 14 participants received a placebo. Behavior was monitored using standardized behavioral metrics as described previously[8]: the caregivers or parents completed the Aberrant Behavior Checklist (ABC) and Social Responsiveness Scale (SRS), and the physicians completed the Autism Clinical Global Impression Severity (ACGI-S) and Autism Clinical Global Impression Improvement (ACGI-I) scales before the intervention, at the 4th, 10th, and 18th weeks of intervention, and then 4 weeks after discontinuing SF or placebo.

Of the 26 participants who were taking SF throughout the study, 17 (65%) improved significantly, most of whom returned to baseline levels 4 weeks after terminating the intervention. None of those on placebo had changed significantly. Individuals randomized to take SF showed improvements in aberrant behavior (measured using the ABC scale) and in social responsiveness (measured using the SRS scale), with a significant decrease in irritability, hyperactivity, and stereotypy. Over the course of the 18-week study, there was a significant increase in communication (as measured by the SRS scale) and an overall improvement on the ACGI-I.

At the conclusion of this study, many parents or caregivers expressed interest in their sons with ASD continuing to receive BSE. We ultimately suggested a small number of commercial nutritional supplements which we had tested to verify that the retail products had levels of active ingredients (SF or its precursor, GR; see Figure 1) close to that which was specified on their labels. Direct comparisons of these products are complicated by the fact that some contain SF and others contain its more stable but biologically inactive precursor, GR (Figure 1). Generally, bioavailability of the GR-rich product averages about 10%, that of GR plus MYR averages about 35%, and for SF-rich BSE it is about 70%, but there is considerable person-to-person variability in bioavailability of any and all of these preparations.[16,17]

## Methods

As reported by parents and caregivers of ASD participants, taking an SF-rich supplement had resulted in improved social responsiveness and communication and had lessened some ASD symptoms such as irritability and motor stereotypies.[8] This was consistent with anecdotal evidence that we continue to receive from people in the ASD community who are familiar with our study and have used various SF preparations. Caregivers of subjects from our published study continued to communicate with us after their formal enrollment in trial had ended and the study results published.[8] One of us (AWZ) called each subject's parent or caregiver in January 2014 to formally ensure accuracy of all follow-up responses, and those comments were confirmed and in some cases updated in the summer of 2016 as we put this manuscript together. There was no prompting for responses. We collected details for presentation herein, as an anecdotal case series. The 4 groups (a–d) into which we have categorized their responses were drawn up *ex post facto*, only after comments had been assembled and not by those who received the responses from caregivers. Of the 44 participants' families in the original study (males from ages 13 to 27 years with moderate to severe ASD) 17 of 26 on SF improved[8]; and 14 of these 17 continued to respond to follow-up questions regarding their progress. Two of the nonresponding subjects on SF also participated in further follow-up. Informed consent was provided by all study participants and/or their caregivers with whom we remained in contact under Protocol # 2011-P-002221/1 by the Partners Human Research Committee at the Massachusetts General Hospital, IND 113542 from the FDA, and NA_00068112 by the Johns Hopkins Institutional Review Board (IRB). A total of 16 families/caregivers responded, and summaries of those responses are reported.

## Results

Responses of the 16 families or caregivers fell into 4 categories. Their sons: (a) experienced no major behavioral changes during the study (n = 3), (b) experienced lasting behavioral changes after administration of the SF supplement and no longer take it (n = 1), (c) they are unsure whether to continue their son on SF because of recent health issues (n = 2), or (d) are either still taking SF (n = 9) or looking to acquire alternative SF supplements (n = 1) (Figure 2).

We begin with an extended narrative from one family about their son whom we have called "R." This is followed by briefer descriptions in accord with the outline (a–d) above. The caregivers' responses are paraphrased, and fictitious single initials are utilized to protect subjects' identities. Responses are truncated or paraphrased herein, and full transcripts are provided as supplemental digital content (see Supplementary Material, Results).

### *R's Story*

R's parents wanted to help him: "He would make constant noises and did all these abnormal motor tics; [we] felt like he really had no control [over his behavior and body] and it was just noise, not functional words. He didn't have any expressive language." R's parents

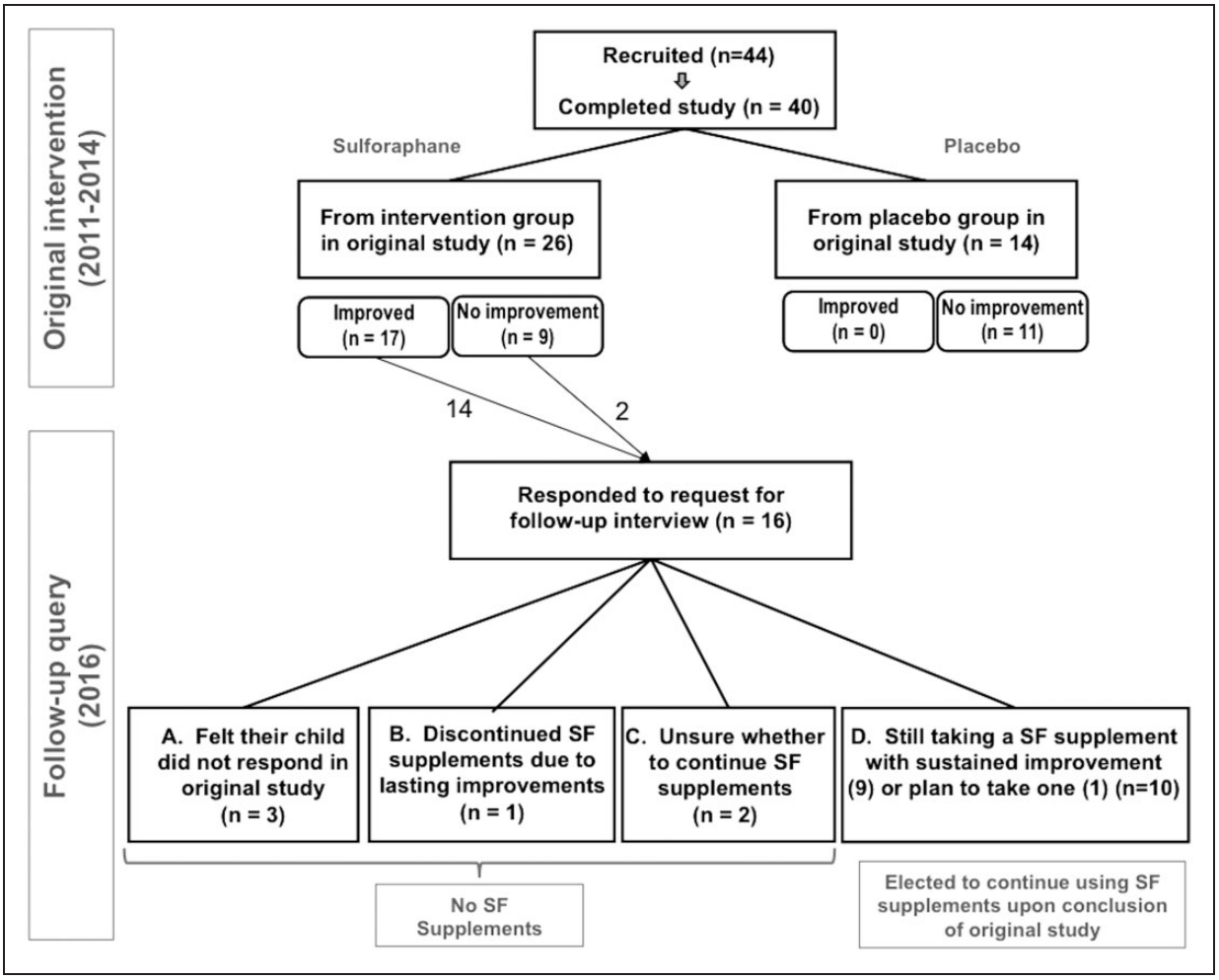


**Figure 2.** Patient Flow for Follow-up Interviews. SF, sulforaphane.

saw several medical specialists who prescribed a total of 18 different medications, all of which had either minimal or negative effects on R. "Nothing changed the constant noises or the terrible rage attacks," until R took SF.

R had taken risperidone, then aripiprazole, but his parents quickly stopped these medications when they realized that they were having negative impacts on their son. On risperidone, R was unable to sleep and became constipated. On aripiprazole, there were improvements in R's sleep pattern, but as soon as he stopped taking it, he began experiencing motor tics. R's family took him to the Lurie Center at Massachusetts General Hospital where we were conducting the study on the effects of SF on males with ASD.[8] The study was a randomized double-blind placebo-controlled trial. However, within days, R's mother believed that he was taking SF: "I knew that he was on the study drug because I saw such a change so quickly. I want to scream from the rooftops and tell people to give the kids broccoli sprouts [extract] because literally, it changed my life," reported R's mother. "Now we can go to the movies, restaurants, plays, we went on vacation with another family, we go to church, we just went to a concert, things we could never do before are now possible. [I am] able to have confidence and he [R] is more confident as well."

N.B. Such a rapid response was unusual in the context of what was observed by the study physicians with other subjects. When responses to supplementation were observed, they generally took 3 or 4 weeks to become manifest. In this case, the study team actually wondered whether the mother might be exhibiting a placebo response; however, the ABC subscales and both ABC and SRS overall scores for R did also change.

## *Summarized Case Reports*

A. Three participants who took SF did not appear to improve during the study. Their parents reported lack of a noticeable effect and were not aware

whether their young adults had been taking SF or placebo.

B. One participant no longer uses SF. However, he improved dramatically while taking it during the study and remained "improved" after the study, suggesting to the study team a possible "epigenetic switch" might have been triggered.

"W is doing fantastic. He really turned into the most relaxed and fantastic child (on sulforaphane). Definitely something great. Helped him a lot. His friends, family, and members at his home all noticed a wonderful change. He is off the sulforaphane and has been since the end of his study in 2012."

C. Two caregivers treated their sons with a BSE supplement and later took them off (n = 2):
   a. "I would like J to go back on the BSE. I have observed a decrease in his eye contact, attention and verbalizing. This could be due to the new medication (levetiracetam) or discontinuing the supplement(?)" [see Supplementary Material.]
   b. "During the study we did see some improvements, mainly his temperament was more even and there were some gains in language. After the study we continued on a sulforaphane supplement and B appeared to do well." [The improvements diminished off the supplement, see Supplementary Material.]

D. Parents of 10 participants reported that their sons are still taking, or plan to take a sulforaphane or a glucoraphanin supplement [BSE]:
   a. "We felt that the broccoli did help our son J have more language. That decreased after the study ended."
   b. "Z continues to take a supplement. Prior to participation in the study, Z had been a fingernail picker, meaning I did not have to trim his finger or toenails for at least 10 years because he would pick at them (keeping them short). Three weeks into the study, I realized that Z's nails needed trimming! And I have had to trim them regularly since, as Z no longer picks at them. My husband and I do feel that Z is a little more verbal, but it is hard to measure that."
   c. P (A nonverbal young adult)—"... is in a group home and comes home every other weekend. The first weekend home after he started the study I noted a change. He was calmer, seemed happier, less stressed. His focus was improved. His group home manager had the same comments about P. She has worked with him since he was 6 years old. I can best describe it as he gained a level or two and it covered all areas; the house manager was in total agreement."
   d. "One of the biggest differences before the study was that he would bite and rip off his shirt. And during the study, he stopped that behavior and it started up again when he was off the sulforaphane. When he was on the sulforaphane, he was more calm and more responsive. M's interactions are more intentional than before."
   e. "He (T) is still on it [BSE]. It's amazing... I don't know what it is. It's almost like voodoo or magic but he is definitely better and he has made improvements."
   f. [Parent of one of the earliest participants—in 2012]—"Before the study, our son utilized speech only for his wants and needs. He did not engage in casual conversation. He did not socialize. His verbal ability was considered 'low' for his age. Within the first month, [after starting study] his teachers noted his speech increasing and his willingness to socialize improving. He began to use articles and prepositions which he had not utilized before... He verbally engaged with our family more than ever before. He initiated casual conversation for the first time. He asked how we felt, what we were doing, and if we needed help (none of which he had done before the study). He showed interest in others, outside of himself."
   g. "R is now happier, has more control over his body, and overall is a positive child with a great attitude. He is more social and goes to concerts, movies, restaurants, vacations, and family outings (all of which were not possible before the study)."
   h. "X is still on sulforaphane and doing well."
   i. J's parents have frequently expressed wonderment to study physicians regarding the effects of SF on their son, who continues to take a BSE supplement.
   j. Son is doing well (and has recently increased BSE intake).

The clinical team, now at the University of Massachusetts Medical School, is currently conducting another clinical trial of SF in 50 boys and girls with ASD, aged 3 to 12 years, (NCT02561481), using a protocol similar to the previous study in young men. In addition to looking for changes in the symptoms of ASD, their collaborators at Johns Hopkins University are evaluating biomarkers in blood samples taken before, during, and after this intervention. They will investigate the molecular mechanisms by which SF brings about changes at the cellular level.

## Discussion

The effects of SF supplementation appear clear and powerful to many caregivers. Their reports are striking.

However, as is usually the case with anecdotal reports, they do not carry the same weight as results from randomized controlled trials or other prospective interventional studies. But, such case histories, chart reviews, and field notes can inspire and instruct formal clinical trials. In this case, they have helped to inspire at least 5 follow-on studies of SF in ASD of which we are aware (NCT02561481, NCT02677051, NCT02909959, NCT02654743, and NCT02879110), and 2 related studies on alleviation of symptoms of schizophrenia (NCT02880462 and NCT02810964).

Commercial sources of the broccoli phytochemicals GR, MYR, and SF are deliberately not mentioned in this article. There are now a large number of products and manufacturers. These manufacturers recommend usage (their label instructions for taking their products) that would theoretically produce a huge range of doses of active ingredient (about 10-fold) if active ingredient content is truly that which is indicated on the labels. We know that between-individual variation in bioavailability (of a known, standardized dose) is also marked. There is no consensus on the appropriate dose for an enhanced healthspan. To the degree that there is any efficacy for specific medical conditions, one can infer an approximate efficacious dose guided by our studies and those of others, but we do not have reliable data on where this dose lies. Our testing of the few products we ultimately recommended to former participants suggests that they do contain what they say they contain, but there are a great many more which we have not tested. There are also many such products that we have tested which do not contain the levels of GR or SF that they claim to contain.

The emotional and economic burdens on the families and caregivers of children and adults with ASD are enormous. In many respects, these caregivers are also in the best position to evaluate ASD symptoms. Evaluation scales such as the ABC depend upon parents' or teachers' observations. Thus, regardless of the fact that any anecdotal evidence elicits disagreements among clinicians over the validity of the observations, it is clear that: (a) ASD cannot be diagnosed as definitively as a fractured leg or an arterial stenosis and (b) if caregivers sense a reduction in symptom intensity, there is direct benefit (to them) that may have intrinsic value. We believe that discussions of the role that nutritional or other ''supplements,'' such as cruciferous vegetables themselves, or the SF-rich and glucoraphanin-rich supplements, can play in the lives of individuals with ASD, is a worthwhile and necessary conversation to have with caregivers. It is also likely that nutritionally based interventions, with demonstrated clinical efficacy, can also contribute to new knowledge about the underlying metabolic pathways that contribute to ASD. We present these case histories in the hope of learning better ways to treat ASD safely and effectively, and stimulating others to do so, thus enhancing the healthspan of the increasing numbers of children that are diagnosed as they progress through life.

Informed consent was obtained under Protocol # 2011-P-002221/1 (Partners Human Research Committee at the Massachusetts General Hospital), IND #113542 (FDA), and NA_00068112 (Johns Hopkins IRB).

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## Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Zimmerman and Talalay are named inventors on a patent (#8937050) pertaining to the treatment of ASD with sulforaphane, the rights to which they have assigned to The Johns Hopkins University School of Medicine.

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## Supplementary Material

Supplementary material is available for this article online.

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